
Processing of time and space in visuo-spatial neglect and the influence of galvanic vestibular stimulation

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Summary

After lesions to the right hemisphere, patients with spatial neglect often exhibit different types of deficits, including temporal, spatial and verticality deficits. Spatial and verticality deficits have been investigated extensively and are both related to the processing of space. Still, little is known about patients' temporal processing deficits. Further knowledge about the nature of temporal deficits and their association with space would not only offer insights into human time processing, but would also be directly applicable to the development of appropriate treatment programs.

Thus, part of this thesis investigated temporal processing in right brain-damaged patients. Deficits in time estimation and bisection of multi-second intervals was found to vary in right brain-damaged patients depending on the presence of spatial deficits. Patients with spatial deficits – independent of whether these were current or previous – showed temporal deficits that were distinct from those of patients without spatial deficits. The compensation of previous spatial deficits did however not entail any improvements of temporal deficits. This implies that improvements in one domain do not necessarily transfer to another domain. Critically, it should not be assumed that temporal deficits will improve merely as a side-effect of treating another deficit. Temporal deficits seem to require an additional, customized treatment program addressing them directly

Galvanic vestibular stimulation (GVS) has recently been proposed as a therapeutic approach for the treatment of neglect patients' deficits. In GVS, electrical current is applied over the mastoids via two opposing electrode poles and can be administered in two different set-ups. GVS leads to polarizing signals in the afferents of the vestibular organs, which are transmitted to a network of cortical areas. The different set-ups of GVS are known to cause different patterns of brain activation and have also been demonstrated to affect spatial and verticality deficits in neglect patients differently. However, it is still unclear which GVS set-up is suitable and most effective for which type of neglect-related deficit. Another open question concerns the effects of GVS after its application. To gain further insights into the aftereffects and the effectiveness of GVS, two experiments and a randomized controlled trial (RCT) were designed.

These experiments provide the first direct evidence of long-term aftereffects of GVS on the subjective verticals across different modalities in both healthy controls and neglect

patients. The results from our RCT on GVS indicated that the simultaneous administration of GVS did not improve spatial deficits in neglect more than standard therapy alone. GVS did however influence the subjective verticals. Depending on its set-up, patients' deviations were ameliorated. In addition to broadening the scientific knowledge of spatial neglect, such research is helpful for a better understanding of the underlying mechanisms of GVS and its use for therapeutic purposes.

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1. Introduction

Hemispatial neglect is a neuropsychological disorder that usually occurs after unilateral damage to the brain. Patients suffering from this disorder can exhibit a variety of deficits, not all of which are well understood yet. Since neglect is known to severely hamper the rehabilitation process further insights into the nature of its different deficits and effective treatments are highly important. The ultimate hope is that a better understanding of neglect would enable the development of treatments which can mitigate the effect of neglect on rehabilitation. This thesis improves our understanding of neglect and its treatment, and takes us a step closer to this goal.

In this introduction, hemispatial neglect and the different types of deficits (temporal, spatial, and verticality) that commonly occur with the disorder are described. Chapter 1.2 is concerned with galvanic vestibular stimulation (GVS) as a therapeutic tool, addressing explanatory models of neglect and related therapeutic approaches, the vestibular system, its stimulation, associated behavioral responses, and brain activation patterns.

1.1 Hemispatial neglect

After unilateral brain damage to temporo-parietal or medial temporal regions, patients often exhibit hemispatial neglect (Husain & Rorden, 2003; Mort et al., 2003). Hemispatial neglect (also known as (spatial) neglect, hemineglect, or unilateral neglect)¹ is defined as the impairment or loss of the ability to detect, respond or orient to sensory stimuli in contralesional space. By definition neglect is not caused by basic sensory and/or motor impairments (Heilman, Valenstein, & Watson, 2000). Such additional impairments do however occur and can be difficult to dissociate (for a summary and frequencies of associated deficits see Kerkhoff, 2001).

Even though neglect can occur after unilateral brain damage to either hemisphere (Beis et al., 2004), left-sided neglect after right hemisphere damage is far more common (Gainotti, Messerli, & Tissot, 1972). This asymmetry seems to be due to a right-

¹ In the following these terms will be used synonymously.

hemisphere dominance for spatial attention. While the left hemisphere directs spatial attention primarily to the left side, the right hemisphere does so for both sides of space (Heilman & Van Den Abell, 1980; Weintraub & Mesulam, 1987) (for a different explanation see Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). The studies included in this thesis investigate neglect after right hemisphere damage, therefore the term ‘neglect’ will from now on refer to left-sided neglect.

Despite its straightforward definition, neglect is a highly heterogeneous disorder that comprises various forms and subtypes. Suggested distinctions are based on the domain (sensory, motor, and mental representation) and the area of space (personal, ultranear, peripersonal, far and imagined) the neglect can occur in. These types are not mutually exclusive, and can thus occur alone or simultaneously with other ones (Kerkhoff, 2001, see also for an overview). Besides the deficits in exploring, estimating, and reproducing space or spatial objects, neglect patients often also exhibit deficits in verticality perception (Funk, Finke, Muller, Preger, & Kerkhoff, 2010; Kerkhoff, 1999; Kerkhoff & Zoelch, 1998; Saj, Honore, Bernati, Coello, & Rousseaux, 2005) and temporal processing (Basso, Nichelli, Frassinetti, & di Pellegrino, 1996; Danckert et al., 2007; Oliveri, Magnani, Filipelli, Avanzi, & Frassinetti, 2013). The nature of these different types of deficits will be discussed in greater detail in the following sections.

Neglect severely hampers the rehabilitation process: it prolongs the time in hospital, leads to poorer functional outcome, less functional improvement per day (Gillen, Tennen, & McKee, 2005), a reduced ability to function in activities of daily living (Di Monaco et al., 2011) and it negatively impacts the regaining of functional mobility in the community (Oh-Park, Hung, Chen, & Barrett, 2014) (for a review see Jehkonen, Laihosalo, & Kettunen, 2006). Effective and easy-to-apply treatments are thus very important.

1.1.1 Temporal deficits

‘Time’ is a broad term that has various meanings and is used in numerous contexts. When discussing time processing, it is therefore necessary to first clarify terminology. In the following time or temporal processing will refer to the explicit encoding or processing of time intervals (in contrast to implicit time encoding during motor activities such as speech or catching a ball) (Grondin, 2010, see also for a review on time perception) (for a review on other temporal deficits in neglect see Becchio & Bertone, 2006).

In everyday life, perception of time intervals can be connected to the past or the future. For instance, when estimating how long some action lasted or will last, or when a certain interval was or will be over. In neglect patients, these temporal estimations are often disturbed. They have difficulties estimating past or future time intervals, e.g. how long they have been waiting for or when a given time interval has elapsed. As a consequence, they often turn up too early or late for their appointments. Since neglect patients usually also have difficulties reading the clock (see 1.1.2. for further details), they can't use this for help. Additionally, neglect patients' estimations of the duration of a given task (e.g. cooking a meal) can be distorted. Patients' deviations on temporal estimations are usually exacerbated when combined with spatial aspects (e.g. estimating the duration or distance of a covered distance) (Kerkhoff, 2004).

Various time processing tasks have been used to examine temporal processing in neglect patients in an experimental setting. Common tasks include: a) verbal estimation of a presented time interval, b) reproduction, in which subjects reproduce the length of a previously presented interval, c) production, in which subjects produce a specified time interval, d) the method of comparison, in which subjects judge the relative interval duration in comparison to another time interval (Grondin, 2010), and e) time bisection, in which subjects indicate half of a previously encoded time interval (Frassinetti, Magnani, & Oliveri, 2009; Oliveri et al., 2009). In the literature 'time bisection' may also refer to a different task (e.g. in Grondin, 2010), but in this thesis it will always refer to the task described above.

Neglect patients show impairments on several of these tasks. They have problems with time production (Basso et al., 1996), time estimation (Danckert et al., 2007), time reproduction and bisection (Oliveri et al., 2009; Oliveri et al., 2013), temporal comparisons (Calabria et al., 2011), and judging the temporal order of stimuli (Snyder & Chatterjee, 2004).

1.1.2 Spatial deficits

Neglect patients' most prevalent deficit is a disturbed exploration of space. Their spontaneous eye and head orientation is deviated about 30° towards the right – even in the absence of a specific task (Fruhmann-Berger & Karnath, 2005). Similar deviations are apparent when patients are explicitly asked to search the entire space (e.g. for specific targets): eye movements are distributed across space only to the right of

patients' sagittal midline (Karnath, Niemeier, & Dichgans, 1998). Such deviations also occur in the dark (Hornak, 1992; Karnath, 1997) and on a tactile search task (Karnath & Perenin, 1998).

Consequences of this disturbed spatial exploration manifest themselves in many activities of daily living: patients may neglect to comb or shave their contralesional side, only eat the food on the right side of the plate, and disregard or bump into persons or objects on their left side (Mesulam, 1981).

Similar left-sided omissions also become apparent when patients are explicitly asked to explore an entire image and report all visible objects (picture scanning), spot specific targets (cancellation task or visuo/tactile search task) or read a text passage (reading task). A large variety of diagnostic tasks exist that reveal and quantify these spatial deficits. These tasks vary in the type and array of the stimulus material, the number of distractors, and the size of the presented stimuli. Task difficulty can also be varied depending on the combination of these different aspects.

Further difficulties of neglect patients emerge when drawing or copying objects. They usually omit the left part of an object, or arrange the numbers on a clock face only on the right side (P. W. Halligan, J. Cockburn, & B. A. Wilson, 1991). This phenomenon has also been observed for words, in that the left half of a word was left out – irrespective of its spatial position. Such deficits have been referred to as object-centered (Kerkhoff, 2001).

Another deficit indicative of neglect is the misjudgment of spatial relations in the left hemifield. When judging distances (Kerkhoff, 2000) and sizes (Barton, Behrmann, & Black, 1998; Bisiach, Pizzamiglio, Nico, & Antonucci, 1996; Halligan, Manning, & Marshall, 1990; Schenkenberg, Bradford, & Ajax, 1980) neglect patients usually judge those on the left side to be larger. The most commonly used task for such misjudgments is the horizontal line bisection task (Schenkenberg et al., 1980). Neglect patients bisect the line too far to the ipsilesional, right side such that the segment on the left side is too long (Barton et al., 1998; Halligan et al., 1990; Schenkenberg et al., 1980).

1.1.3 Verticality deficits

Humans' sense of verticality is constructed by integrating vestibular, somatosensory and visual input (Barra et al., 2010). Despite this integration of several sensory signals, the

internal estimate of verticality can be assessed by different methods, testing preferentially one modality: the visual, the tactile and the postural. In the following these will be referred to as the subjective visual (SVV), subjective haptic (SHV) and subjective postural vertical (SPV) respectively. The SVV, SHV and SPV can be assessed in three spatial planes (frontal, sagittal, horizontal). The spatial planes are also referred to in terms of rotations around the axis (x, y, z) or the actual rotational movements (roll, pitch, yaw) (Fig.1).

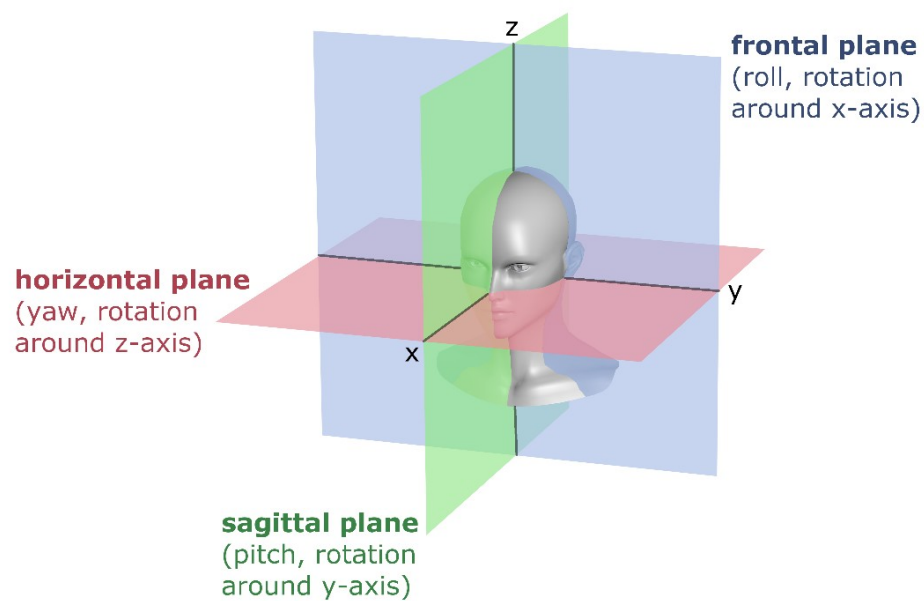


Figure 1 Diagram illustrating the three spatial planes

In neglect patients, verticality perception is often disturbed in all three planes. In the horizontal plane, subjects are typically asked to indicate their subjective straight ahead (SSA) by pointing their arm or indicating (motoric or verbally) a stimulus (e.g. rod, laser pointer) to where they feel the straight ahead of their body is. The SSA of neglect patients is typically shifted to the right, ipsilesional side in the visual and tactile modality (Heilman, Bowers, & Watson, 1983; Karnath, 1994b; Karnath & Perenin, 1998; Richard, Rousseaux, Saj, & Honore, 2004; Rossetti et al., 1998). In the frontal and sagittal plane, patients are also asked to indicate when they perceive a visual line or a rod as vertical. Standardized methods for the SVV are for instance a computer program for the analysis of visual-spatial perception (VS) (Kerkhoff & Marquardt, 1995), and the bucket method (Zwergal et al., 2009a). Devices to measure the SHV consist of a rod that is rotatable

around the to-be-measured axes and are usually designed and built by its users to meet their specific needs. In both the visual and tactile modality, neglect patients exhibit contralesional (or counterclockwise) deviations in the frontal (Braem, Honore, Rousseaux, Saj, & Coello, 2014; Kerkhoff, 1999; Kerkhoff & Zoelch, 1998), and backwards (that is towards the patient) deviations in the sagittal plane (Funk, Finke, Muller, Preger, et al., 2010; Saj, Honore, Bernati, et al., 2005; Utz, Keller, Artinger, et al., 2011). These SVV and SHV judgments are greatly influenced by both external and internal factors. Depending on their nature, context information, head position and posture can either alleviate or worsen patients' deviations (Funk, Finke, Muller, Preger, et al., 2010; Funk, Finke, Muller, Utz, & Kerkhoff, 2011; Funk et al., 2013; Saj, Honore, Davroux, Coello, & Rousseaux, 2005).

Interestingly, verticality adjustments became more reliable when visual and haptic information was integrated in a visuo-spatial vertical task than with unimodal adjustments (Braem et al., 2014). This was found for healthy controls, as well as right brain-damaged patients with and without neglect.

Overall, SVV deviations seem to be greater and more variable in patients with unilateral brain damage and were specifically associated with neglect (Yelnik et al., 2002). Both neglect and hemianopia similarly exacerbated visuo-tactile verticality deviations, and had additive effects when combined (Saj, Honore, Bernati, & Rousseaux, 2012). Moreover, patients' ambulation performance and the severity of neglect also correlates with SVV and SHV deficits (Kerkhoff, 1999). A recent study, however, found that neglect severity is only related to the uncertainty intervals of verticality estimations, but not to the actual size of the deviations (Funk, Finke, Muller, Preger, et al., 2010). In addition to deviations in verticality, neglect patients also exhibit impairments in posture. Until now, the SPV of neglect patients has only been assessed in the frontal plane. In general, right brain damage seems to be related to lateral displacements towards the contralesional side in standing (Rode, Tiliket, Charlopain, & Boisson, 1998) and sitting (Saj, Honore, Bernati, et al., 2005). Neglect patients show a contralesional tilt of their postural vertical that is modulated by neglect severity (Lafosse, Kerckhofs, Troch, Santens, & Vandenbussche, 2004; D. A. Perennou, Amblard, Leblond, & Pelissier, 1998). They also seem to have general difficulties with postural stability (D. Perennou, 2006).

1.2 Galvanic vestibular stimulation as a therapeutic tool

1.2.1 Neglect theories & stimulation techniques

Since the discovery of neglect, several ideas and theories have been proposed to explain its occurrence. In their original form, these theories were developed to explain patients' spatial and verticality (but not temporal) deficits. Generally, these theories can be divided into four main groups: attentional, representational, cerebral balance and transformational theories (Kerkhoff, 2001). Since transformational theories have prompted the development of several therapies and are also the basis for GVS, they will be described in greater detail here.

Transformational theories are based on the concept of reference frames. A given reference frame represents the spatial location of an object, stimulus, or body part from a particular perspective. Spatial locations in relation to the subject itself are represented in an egocentric, or body-centered reference frame (Vogelely & Fink, 2003). The brain constructs such an egocentric reference frame from sensory input information and transforms it into motor output information. In neglect, this transformation is assumed to be impaired or biased (Jeannerod & Biguer, 1989). Both Vallar (1997) and Karnath (1997) suggested that this transformation works with a consistent error to the ipsilesional side of space causing a deviation of the spatial reference frame. While Vallar (1997) assumed a translation of the midsagittal body axis, Karnath (1997) postulated a rotation around the body's midline.

Based on this theoretical framework of a disturbed spatial transformation in neglect, sensory stimulation techniques were developed. Spatial coordinates necessary to construct the egocentric, body-centered frame of reference are provided by multiple sensory channels. Accordingly, it is assumed that when the input of a given sensory channel is manipulated, neglect behavior should change (Karnath, 1994a). Indeed, such stimulation techniques targeting different input channels have been found to effectively ameliorate neglect (for a review see Kerkhoff & Schenk, 2012). GVS is such a stimulation technique and targets the vestibular channel. To better understand its effects and underlying mechanisms, the vestibular system will be described in the following chapter.

1.2.2 The vestibular system

The vestibular system encodes angular, linear and gravitational accelerations of the head in space and thereby provides the brain with information of three-dimensional head movements and gravity. Vestibular signals are closely related to oculomotor and postural reflexes and are thus crucial for motion perception (self vs. object motion), eye movements, postural control, spatial cognition, and gravity perception (Eickhoff, Weiss, Amunts, Fink, & Zilles, 2006; Lopez, Blanke, & Mast, 2012, see also for a review).

At the receptor level, each of the two vestibular organs consist of two functional units: the otolith organs and the semicircular canals. For each vestibular organ, there are three semicircular canals which are named according to their orientation: anterior, posterior, and horizontal canal. They are aligned orthogonally to each other, so that each canal is sensitive to rotation in its associated spatial plane. The magnitude of an acceleration is coded by the activity difference of parallel pairs of canals on the left and right side of the head. Thus, the semicircular canals can reconstruct any three-dimensional rotational movement and are responsible for tracking rotations of the head (Day & Fitzpatrick, 2005a; Jay M. Goldberg et al., 2012, p. 23).

The other functional unit, the otolith organ, is divided into two subunits: the utricle and the saccule. They are also oriented orthogonally to each other: the utricle horizontally, the saccule parasagittal. Both otolith organs are sensitive to linear accelerations directed parallel to their surface. Accordingly, the utricle senses forces in the head's horizontal plane and the saccule forces in the frontal plane. The acceleration magnitude is encoded by the firing rates of the primary vestibular nerve fibers. Besides encoding the head's translations, the otolith organs also sense gravitational forces. Thus, they signal the position of the head with respect to the earth vertical, including head tilt (Jay M. Goldberg et al., 2012, p. 94)

The signals from both the semicircular canals and the otoliths are transmitted via the axons of the ganglion cells, which are projecting to four vestibular nuclei located in the brainstem (Jay M. Goldberg et al., 2012, p. 138). From there, further projections reach the thalamic nuclei (Lopez & Blanke, 2011). The thalamus not only relays information from the periphery to the cortex (Behrens et al., 2003), but is also involved in the processing of the vestibular signals itself (Lopez & Blanke, 2011). The exact role of the thalamus in vestibular processing is not entirely clear. It has been suggested in various functions ranging from cortico-cortical communication, sensorimotor modulation, over

distinguishing head translations and tilts, to the integration of vestibular, visual, somatosensory and motor signals. Subsequent projections from the thalamus lead to numerous cortical areas (Lopez & Blanke, 2011, see also for a review).

1.2.2.1 Vestibular cortical areas

While the nuclei and connections at the level of the brainstem are well investigated, the exact localization of vestibular processing in the cortex is still not entirely clear. The first studies were conducted with primates and found an extensive cortical area related to vestibular processing: the so-called parietal insular vestibular cortex (PIVC) (Grusser, Pause, & Schreiter, 1990a, 1990b). It includes parts of the granular insula and the retroinsular region. The PIVC was regarded as the core region of a network of vestibular cortical areas (Guldin & Grusser, 1998). Since a PIVC was found in three different primate species, the existence of a similar area was also predicted for the human brain (Guldin & Grusser, 1998).

Although numerous studies have used advanced, neuroimaging methods to address cortical vestibular processing, the existence and precise location of a human homologue of the PIVC is still under debate. Due to the use of different vestibular stimulation methods that activate different parts of the vestibular organs, slightly different brain activation patterns have been found (Lopez et al., 2012, see also for a detailed description on the different methods). To examine the overlap between activation patterns of previous neuroimaging studies, two groups conducted meta-analyses (Lopez et al., 2012; zu Eulenburg, Caspers, Roski, & Eickhoff, 2012).

One study found the area OP2, which is located “at the junction of the posterior parietal operculum with the insular/retroinsular region” (Eickhoff et al., 2006, p. 612), to have the greatest convergence across different stimulations. It was also connected with all other active areas found. The authors suggested that OP2 might in fact be an exclusively vestibular area. Other areas that were reported as active were the temporo-parietal cortex, lateral and medial premotor cortex, and parts of the insula (zu Eulenburg et al., 2012). The other meta-analysis by Lopez et al. (2012) identified the insula, the parietal operculum and the retroinsular cortex (which is immediately posterior to OP2) as active in all forms of vestibular stimulation. They concluded that afferents from the otoliths and semicircular canals converge in these regions. Functionally, these regions might be involved in body rotations, translations and tilts.

The aforementioned findings are supported by a study combining functional magnetic resonance imaging (fMRI) with cytoarchitectonic mapping. Here, the posterior parietal operculum was also identified as a crucial area for vestibular processing. More specifically, the area OP2 was proposed as the human homologue of the PIVC due to its functional and topographical characteristics. It is located in a similar area as the PIVC (medially and reaches into the retroinsular region) and OP2's cytoarchitectonics suggest it as a primary sensory area since the cells are distinct from its surrounding (Eickhoff et al., 2006).

In addition to this circumscribed region activated by various vestibular stimulation techniques, there are various other cortical areas also receiving vestibular input. Since these areas also include primary sensory areas from other sensory modalities, the 'vestibular cortex' (or rather cortices), if one exists, is considered to be multi-sensory. Signals from the vestibular organs are integrated with other sensory signals as early as the brainstem, so that vestibular input to the cortex is also largely multi-sensory (Guldin & Grusser, 1998). The vestibular cortices comprise the following areas: the temporo-parieto-insular and retroinsular cortex, parietal cortex (intraparietal sulcus region & inferior parietal lobule), frontal cortex (including the primary motor cortex), cingulate cortex, and three subcortical structures (thalamus, basal ganglia, and cerebellum) (Lopez et al., 2012).

1.2.2.2 Lateralization of vestibular processing

While other sensory system are strongly lateralized in the hemisphere contralateral to its sensory receptors, the cortical network of the vestibular system is distributed differently. The projections from the vestibular organs to the cortex are bilateral, but with two preponderances. First, any dominance in vestibular processing is determined by subjects' dexterity: right-handers have a vestibular dominance in their non-dominant right hemisphere, while the opposite is the case for left-handers. Secondly, the afferents of the vestibular organ predominantly project to the ipsilateral hemisphere (Dieterich et al., 2003). While the first evidence for these preponderances stems from semicircular canal stimulation (Dieterich et al., 2003), it was also confirmed for stimulation of the otoliths (Janzen et al., 2008). Moreover, these findings were supported in two meta-analyses (Lopez et al., 2012; zu Eulenburg et al., 2012).

Such preponderances are crucial for determining brain activation patterns, behavioral responses and therapeutic approaches of vestibular stimulation techniques.

1.2.3 Vestibular stimulation

There are different forms of vestibular stimulation, besides the activation by actual movements that can be experimentally manipulated. There are acoustic click signals (inducing vestibular evoked myogenic potentials, VEMPs) (Janzen et al., 2008), caloric irrigation and GVS. These methods directly stimulate parts of the vestibular organs or nerves, although they are non-invasive techniques. Since caloric irrigation has also been used as a therapy for neglect, it will be described briefly.

Caloric irrigation was already developed at the beginning of the 20th century and has been widely used for research and diagnostic purposes. The technique involves irrigation of the external auditory canal with cold or warm water thereby exciting the semicircular canal receptors and their vestibular afferents (for a review see Been, Ngo, Miller, & Fitzgerald, 2007). As a treatment for neglect, caloric irrigation was found to improve left-sided exploration (Adair, Na, Schwartz, & Heilman, 2003; Rode & Perenin, 1994; Rubens, 1985; Sturt & David Punt, 2013) and anosognosia (Cappa, Sterzi, Vallar, & Bisiach, 1987; Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990) after caloric irrigation of the contralesional ear.

Unfortunately, caloric irrigation can cause side effects like vertigo, nausea or vomiting (Been et al., 2007). GVS, on the other hand, lacks such adverse effects, is well tolerated (Utz, Korluss, et al., 2011) and is easy to apply. In GVS, electrical currents are transduced via rubber electrodes which are put into saline-soaked sponges and placed on the mastoids. The two electrodes are of opposite polarity (anode and cathode) and can be set-up in several, different ways: bilateral monopolar (two same pole electrodes on each mastoid and a reference site further off), unilateral monopolar (one pole on one mastoid and a reference site), and bilateral bipolar (the anode and cathode on the mastoids) (Fitzpatrick & Day, 2004). The studies conducted as part of this thesis all investigated effects of bilateral, bipolar GVS. For this form of stimulation, there are two possible set-ups: left-cathodal/right-anodal GVS (CL-GVS) and right-cathodal/left-anodal (CR-GVS).

1.2.3.1 Neuronal effects and pathways

In humans, the direct currents that are delivered via the electrodes during GVS are assumed to lead to polarization effects in the primary afferents of both the semicircular canals and the otoliths (Fitzpatrick & Day, 2004). Direct evidence of GVS effects at the vestibular organs and the ascending pathways to the cortex stems only from animal studies. GVS was found to directly influence the discharge of the primary afferent axons by acting close to the postsynaptic trigger site. Thus, it seems to bypass the receptors of the vestibular system. In the afferents, anodal currents decreased and cathodal currents increased the firing rate (J. M. Goldberg, Fernandez, & Smith, 1982). Interestingly, the afferents affected by GVS are mainly irregular ones. Irregular afferents make up about $\frac{1}{4}$ of the primary afferents and have distinct properties that make them sensitive to small currents. They have a lower tonic rate, a greater response to excitatory stimuli, a shorter refractory period and are more sensitive to acceleration stimuli. The irregular afferents mainly innervate the spinal-projecting secondary neurons. Regular fibers on the other hand mainly project to oculomotor-projecting neurons. The cerebellar-projecting units are innervated by both regular and irregular fibers (Fitzpatrick & Day, 2004; J. M. Goldberg et al., 1982; J. M. Goldberg, Smith, & Fernandez, 1984).

These findings from animal research are largely assumed to also be true for humans. There is also some indirect evidence from investigations on GVS effects in humans. The evidence is indirect, in that the observed GVS-induced reactions, are not recorded from vestibular afferents. Conclusions about which parts of the vestibular organs are activated by GVS are drawn instead from the behavioral, primarily oculomotor responses detected. While eye torsions reflect otolith stimulation, nystagmus is related to semicircular canal stimulation. Depending on stimulation parameters, both types of eye movements were observed during GVS (Severac Cauquil, Faldon, Popov, Day, & Bronstein, 2003). Thus, it appears that both otoliths and semicircular canals are activated during stimulation. This is also supported by investigations of vestibular patients (H. G. MacDougall, Brizuela, Curthoys, & Halmagyi, 2002). Despite these findings, it is still debated whether the oculomotor responses are mainly driven by one (Cohen, Yakushin, & Holstein, 2011, 2012; Schneider, Glasauer, & Dieterich, 2000) or both parts of the vestibular organ (Curthoys & Macdougall, 2012).

1.2.3.2 Brain activation

From the peripheral afferents, the GVS-induced signals are transmitted further to cortical areas (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Lobel, Kleine, Bihan, Leroy-Willig, & Berthoz, 1998). In terms of its therapeutic application, it is very important to not only know which cortical areas are activated by GVS, but also whether there are any differences in cortical activity depending on the different set-ups of GVS (see chapter 1.2.3 for details).

Overall, there is agreement that GVS activates a broad network of areas within the brain. Activity increases were found in the following areas: parts of the insula, inferior parietal lobule (including the temporo-parietal junction), the superior and transversal temporal gyrus, the precentral gyrus, the middle frontal gyrus, the anterior cingulate gyrus, the intraparietal sulcus, the paramedian and dorsolateral thalamus, and the putamen (Bense et al., 2001; Bucher et al., 1998; Lobel et al., 1998; Lobel et al., 1999; Stephan et al., 2005). Deactivations were reported for the transverse frontopolar gyrus, parieto-occipital areas and the majority of visual cortex (Bense et al., 2001; Lobel et al., 1998). As mentioned earlier, vestibular signals are closely associated and also integrated with signals from other senses. Some of the brain areas activated by GVS are related to ocular motor function or somatosensory processing (Bense et al., 2001).

Findings regarding any distinctions between different GVS set-ups are mixed: while one study on GVS-induced brain activation did not find any differences depending on the polarity set-up of the electrodes (Bense et al., 2001), two ensuing studies did (Eickhoff et al., 2006; Fink et al., 2003). A CL set-up, that is assumed to stimulate the left vestibular nerve and inhibit the right, led to activation in both hemispheres. CR-GVS on the other hand, stimulating the right and inhibiting the left vestibular nerve, led to unilateral, right hemisphere activity. Interestingly, the first study using fMRI and GVS is consistent with these later findings: CL-GVS activated the vestibular network bilaterally (Bucher et al., 1998). However, these findings only apply to right-handed subjects. Left-handed subjects and their GVS-induced brain activation has not been investigated yet. Based on the study by Dieterich et al. (2003) using caloric irrigation, it can be hypothesized though that CL-GVS would mainly lead to left hemisphere activity, and CR-GVS to bilateral activation. It is however up to future research to confirm this. While GVS-induced activity patterns are polarity specific, they are not dependent on the frequency of the current (Stephan et al., 2005).

These polarity specific effects imply that CR-GVS could alleviate neglect patients' spatial deficits by activating the right hemisphere and directing attention to the left hemispace again.

1.2.3.3 Behavioral and perceptual responses

Besides the set-up of GVS, subjects' head position and the associated position of the vestibular organs should also be considered since they are crucial for the perception that is induced by GVS. Fitzpatrick and Day (2004) proposed a vector model to predict GVS-induced perceptions. The model is based on the anatomical position of the semicircular canals and assumes similar modulation of each canal's firing rates (St George & Fitzpatrick, 2011). When summing up the vectors of all canals, the resulting net vector indicates around which axis the perception rotates. The movement direction is determined by the electrode poles: away from the anode/towards the cathode. According to the model, the net rotational vector of, for instance CL-GVS with the head in an upright position, would be directed posteriorly and inclined upwards, with a large component in the frontal plane and a smaller component in the horizontal plane – directed towards the cathode on the left side. The component in the sagittal plane would be cancelled out. In this model, the otolith organs are expected to only produce a very small signal due to signal cancellation of the two parts of the utricle (pars lateralis and medialis): a linear, lateral acceleration towards the cathode or tilt towards the anode. Due to lack of empirical data, the saccules' signals are not modeled (Fitzpatrick & Day, 2004). This model is supported by behavioral data of healthy subjects (Day & Fitzpatrick, 2005b) and self-reports from subjects with their head upright during GVS: a sensation of body tilt in the frontal (72%) or horizontal (18%) plane, which was mainly perceived for the head (Lenggenhager, Lopez, & Blanke, 2008).

Besides inducing a perception of head motion, GVS also causes detectable oculomotor and postural responses. In the oculomotor domain, GVS causes both eye rotations and nystagmus (slow phase) in the direction of the anode (Severac Cauquil et al., 2003; Watson et al., 1998; Zink, Bucher, Weiss, Brandt, & Dieterich, 1998). Despite of a considerable inter-subject variability, these oculomotor responses are highly replicable within subjects (H.G. MacDougall, Brizuela, Burgess, & Curthoys, 2002) and have also been observed with currents as low as 0.9 mA (Severac Cauquil et al., 2003). In terms

of their magnitude, responses did not differ depending on polarity and laterality (i.e. where cathode and anode are placed) (H. G. MacDougall, Brizuela, & Curthoys, 2003). In standing subjects with an upright head, GVS causes sway towards the side of the anode (Britton et al., 1993; Nashner & Wolfson, 1974). It appears to be a reflexive balance response to the GVS-induced signal of head movement that is mediated via vestibulo-spinal reflexes (for a review see Fitzpatrick & Day, 2004; Wardman, Taylor, & Fitzpatrick, 2003). The sway is modulated by several factors: head position (Nashner & Wolfson, 1974), body position (standing vs. seating) (Britton et al., 1993), the standing surface and body posture (legs apart vs. together vs. in a 'tandem' position) (Wardman, Day, & Fitzpatrick, 2003; Wardman, Taylor, et al., 2003). Recently, this sway response was reliably assessed with different markers and found to be highly replicable across a large sample. The response magnitudes tended to decrease with increasing age (Tax et al., 2013). Contrary to that, head movements in the horizontal plane – induced when the head is tilted forward – do not require a balance, but an 'orientation' response: orienting the body towards the left or right side of space. Indeed, subjects turn towards the side of the anode when perceiving a GVS-induced head movement in the horizontal plane and do not exhibit any sway (St George & Fitzpatrick, 2011).

1.2.3.4 Suitability for clinical studies and safety issues

GVS has been used extensively for research purposes (for a review see Fitzpatrick & Day, 2004). To be considered as a therapy that is applied over prolonged time periods and possibly repetitive, however, the safety of GVS must also be considered.

Safety parameters for direct current stimulation were mainly investigated for transcranial direct current stimulation (tDCS). In tDCS the electrodes are placed directly on the scalp to stimulate underlying cortical areas (Utz, Dimova, Oppenlander, & Kerkhoff, 2010). Besides the electrode placement, GVS and tDCS rely on the same electrical and physiological mechanisms. Parameters are thus assumed to be similar for the two methods.

There are two parameters regarded as important for single session tDCS: current density (stimulation strength (A)/electrode size (cm²)) and total charge (stimulation strength (A)/electrode size (cm²) x total stimulation duration). While current density itself is independent of stimulation duration, the total charge takes the duration into account (Nitsche et al., 2003). Nitsche et al. (2003) recommend current densities below 0.02857

mA/cm² and found no heating under the electrodes with this criterion (Nitsche & Paulus, 2000). Another group stimulated with 1 and 2mA for 20 minutes and found densities up to 0.08 mA/cm² to be safe (Iyer et al., 2005). Despite adhering to these safety limits, there were some later reports of skin lesions at electrode site after tDCS (Frank et al., 2010; Lagopoulos & Degabriele, 2008; Palm et al., 2008). Since there was no evidence of any neuronal damage (Nitsche & Paulus, 2001) or changes in cerebral tissue and the blood-brain-barrier though (Nitsche et al., 2004), stimulation up to 2 mA over a maximum of 20 minutes are currently considered safe.

These values have also been adopted for GVS. Recently, some studies have also investigated side effects of GVS. In most studies a self-reporting questionnaire on possible side effects and sensations was administered. In two studies with healthy controls and currents from 1-2mA, 81% and 91% of subjects reported mild to moderate pain (at the site of the anode) or heat sensations at electrode site (75%). Other frequently reported side effects were: general discomfort (55-75%), mild vertigo (55-63%), nausea (63%), eyestrain (55%), blurred vision (36%), headache (36%), head fullness (36%) and difficulty concentrating (36%) (Lenggenhager et al., 2008; Lopez, Lenggenhager, & Blanke, 2010). Besides these findings on healthy controls, two studies on patients reported significantly less adverse side effects. In 255 sessions of GVS in 55 stroke patients and 30 healthy subjects, Utz et al. (2011) found no adverse side effects in 62.2 %. There was only 1 case of severe headache and otherwise mild tingling during (15.3%) and itching during (16.5%) and after (11.8%) stimulation. Most subjects received sub-sensory stimulation (mean of 0.6 mA), but the only difference in side effects to patients being stimulated at 1.5 mA for 15-20 minutes was more frequent itching and tingling. Importantly, healthy controls, right brain-damaged patients with and without neglect did not differ regarding the report of side effects (Utz, Kroluss, et al., 2011). Consistent with these findings, a case study using repetitive GVS on five consecutive days only found increased saliva production and occasional redness at the electrode sites. The patient himself did not report any uncomfortable side effects (Wilkinson, Zubko, & Sakel, 2009). To summarize, GVS appears to be safe, well tolerated, easy and inexpensive to apply. An additional advantage for clinical studies is that sham stimulation is not distinguishable from real stimulation. Subjects reported the same amount of itching and mild headache for both stimulation conditions and were not able to distinguish the two (Gandiga, Hummel, & Cohen, 2006). Such comparability between sham and real stimulation allows for performing a blinded trial. Accordingly, the results are less likely to be biased by

patients' knowledge of the treatment they are receiving, which increases the explanatory power of an investigation. Moreover, GVS is suitable for repetitive treatment and can be applied while another task or therapy is performed.

1.3 Rationale of the thesis

A better understanding of the nature of neglect patients' different types of deficits and how these are affected by GVS – both during and after its application – is highly important not only for obtaining further insights into the mechanisms of GVS, but also for customizing the use of it for therapy to the individual patient's needs. Since neglect severely hampers the rehabilitation process (Di Monaco et al., 2011; Gillen et al., 2005; Jehkonen et al., 2006; Oh-Park et al., 2014), effective treatments for the different deficits are needed to enhance patients' recovery.

While spatial and verticality deficits in neglect have been investigated quite extensively, temporal deficits in neglect are less well understood. Time estimation is often disturbed in neglect patients in everyday life in the clinic, but has only been investigated in one study (Danckert et al., 2007). It is however not clear whether those results were biased by the stimulus material used (numbers & illusory motion). On time bisection tasks, neglect patients' deviations resemble those on a spatial bisection task (Oliveri et al., 2009; Oliveri et al., 2013), indicating a close association between spatial and temporal deficits. A close association between spatial and temporal deficits could have important implications for therapy, in particular regarding the transfer of improvements from one domain to the other. Consequently, in study 1 time estimations and bisections in the suprasecond time range were investigated for three different groups of right brain-damaged patients (with spatial neglect, without spatial neglect, with a previous history of neglect) as well as a healthy control group.

By now, there are already a few studies indicating that GVS affects both spatial and verticality perception. The findings on spatial deficits in neglect are however mixed. While most studies reported improvements during CR-GVS (Rorsman, Magnusson, & Johansson, 1999; Utz, Keller, Kardinal, & Kerkhoff, 2011; Wilkinson et al., 2009; Zubko, Wilkinson, Langston, & Sakel, 2013), one study also demonstrated improvements during CL-GVS (Utz, Keller, Kardinal, et al., 2011). Ameliorations were also found during CL-GVS for neglect patients' contralesional shifts of the subjective vertical (Saj, Honore, & Rousseaux, 2006). While these studies only investigated effects *during* GVS, two recent

studies showed that an improved spatial exploration also lasted until *after* the application of CR-GVS (Wilkinson et al., 2014; Zubko et al., 2013). However, opposite effects *after* GVS have been reported for oculomotor responses (H.G. MacDougall et al., 2002; H. G. MacDougall et al., 2003; Severac Cauquil et al., 2003; Watson et al., 1998; Zink et al., 1998) and movement perceptions (St George, Day, & Fitzpatrick, 2011).

To further investigate GVS aftereffects on different types of deficits and the effectiveness of both a CR- and a CL-set-up, two experiments were conducted. Study 2 was designed to examine aftereffects of GVS for the subjective verticals. The subjective visual, haptic and postural vertical were assessed during and after GVS, in both healthy controls and right brain-damaged patients with neglect. Study 3 was a randomized controlled, double-blind trial to study the effectiveness of GVS for the treatment of spatial and verticality deficits in neglect. The intervention was administered in an add-on design with three different treatment conditions: standard therapy was either combined with CL-GVS, CR-GVS, or Sham-GVS. Different spatial tasks and the subjective visual and haptic vertical were assessed immediately, two and four weeks after the intervention period.

2. Individual projects

2.1 Time estimation and bisection of multi-second intervals in right brain-damaged patients

2.1.1 Introduction

Recently, neglect patients were shown to deviate not only on the bisection of physical, but also temporal intervals. When asked to set the midpoint of a previously presented time interval (time bisection) by reproducing half of the interval, neglect patients showed a lateralized bias. They set the midpoint forward in time compared to the true midpoint (Oliveri et al., 2009; Oliveri et al., 2013). This seems to mimic the rightward error made in spatial tasks such as line bisection (Schenkenberg et al., 1980). Oliveri et al. (2013) suggested that these lateralized deviations indicate an underestimation of time: setting the midpoint later in time assumes that time elapses slower, thus causing an underestimation. In line with that, Danckert et al. (2007) found that right brain-damaged patients with neglect severely underestimated multi-second time intervals. These underestimations were found for an illusory motion stimulus with a secondary task using numbers. Several studies have shown though that numbers influence temporal processing (Brown, 1997; Cappelletti, Freeman, & Cipolotti, 2009, 2011; Dormal, Seron, & Pesenti, 2006; Oliveri et al., 2008). Interestingly, on a time reproduction tasks, neglect patients performed as well as right brain-damaged patients without neglect. It should however be noted that the aforementioned studies differed in the type and length of their employed stimulus material. Thus, two questions remain unclear: 1) Do right brain-damaged patients underestimate time intervals also with non-numerical stimulus material?, and 2) Do their time bisection deficits also occur for multi-second intervals longer than 2.4s?

Another still debated issue is the relationship between time and space processing. Since the ATOM's ('A Theory of Magnitude') proposal of similar, partly shared principles and neural substrates for the processing of different magnitudes, including time, space and numbers (Walsh, 2003), numerous studies investigated this claim. In support of this,

studies reported a changed temporal perception when spatial information was either merely present (R. Bottini & Casasanto, 2010a; Casasanto & Boroditsky, 2008; Casasanto, Fotakopoulou, & Boroditsky, 2010; Xuan, Zhang, He, & Chen, 2007) or even manipulated (Frassinetti et al., 2009; Magnani, Oliveri, Mancuso, Galante, & Frassinetti, 2011; Magnani, Pavani, & Frassinetti, 2012; Oliveri et al., 2013; Vicario, Caltagirone, & Oliveri, 2007; Vicario et al., 2008). Based on neurological cases, two different processing routes were suggested for time and space: one with independent mechanisms for each dimension and another one in which both time and space interact (Cappelletti et al., 2009, 2011). There are indications for the interaction to be asymmetric, in that temporal processing can be hampered by other dimensions (i.e. numbers) but not vice versa (R. Bottini & Casasanto, 2010b; Cappelletti et al., 2009, 2011; Dormal et al., 2006; Droit-Volet, Clement, & Fayol, 2003).

Deficits in time processing – especially when spatial encoding is encouraged – were associated with deficits in spatial processing (Basso et al., 1996; Danckert et al., 2007; Oliveri et al., 2009; Oliveri et al., 2013). In terms of interactions between time and space, we were interested in patients' temporal processing after previous spatial deficits are largely compensated for. Such findings could possibly shed some further light onto the different processing routes and their interaction.

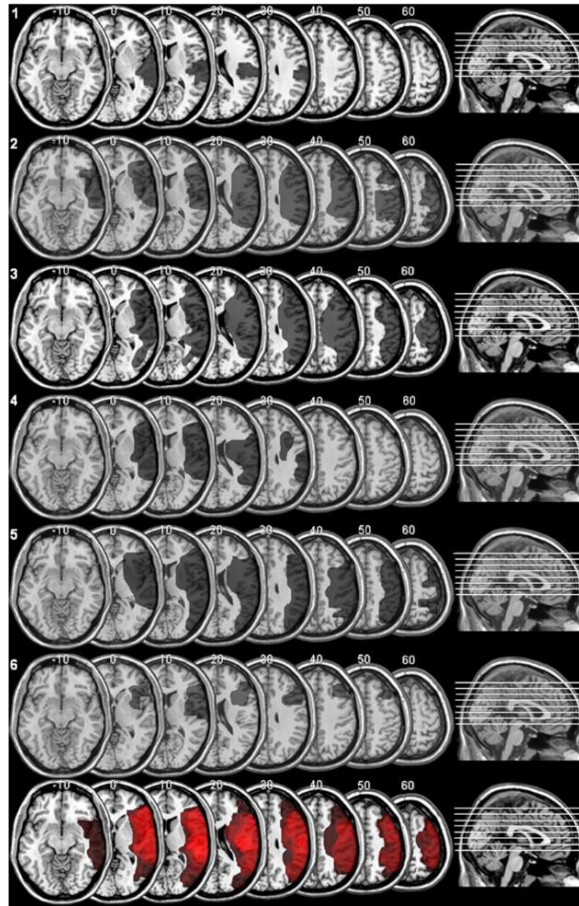
Accordingly, we tested right brain-damaged patients with spatial neglect, without spatial neglect, with a previous history of neglect and in healthy controls on time estimation and bisection of multi-second intervals (6-24s) to answer the following questions: 1) Do right brain-damaged patients underestimate time intervals also with non-numerical stimulus material?, 2) Do their time bisection deficits also occur for multi-second intervals longer than 2.4s?, and 3) How are they processing time after compensating previous spatial deficits and are there any associated differences in lesion location?

2.1.2 Material and Methods

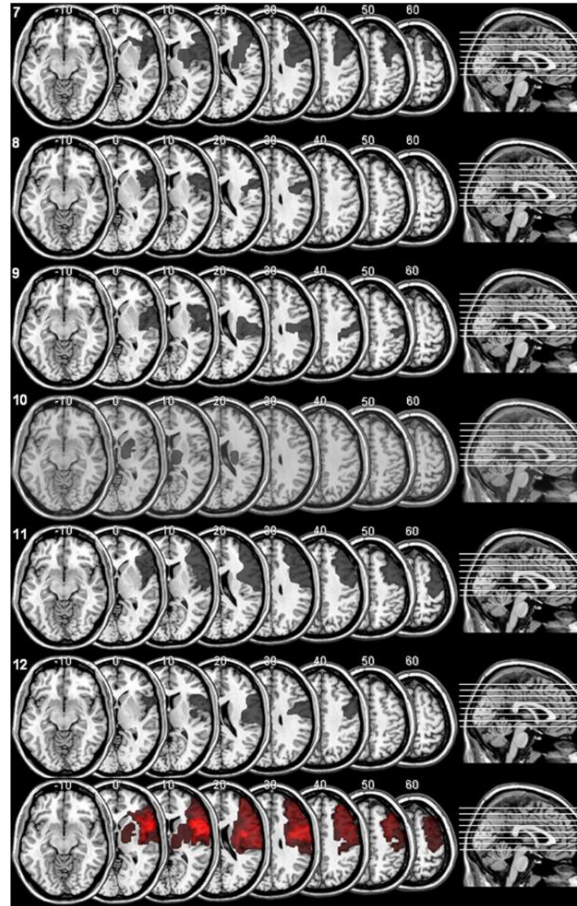
Subjects

18 right brain-damaged patients and six healthy controls participated in the study after providing their written informed consent. The ethics committee of the Ludwig-Maximilians-University approved this study. Patients were recruited from the Schoen

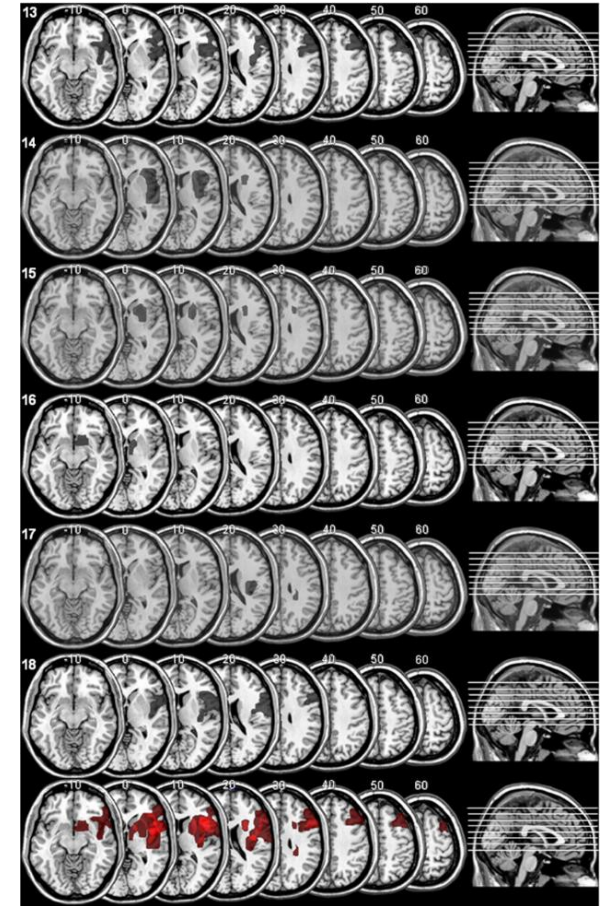
Klinik Bad Aibling. All patients had unilateral lesions due to cerebrovascular accidents, confirmed by CT/MRI scans. Lesioned areas were mapped onto a standard MRI template using MRICron software (Rorden & Brett, 2000) (Fig.2). Gender, age, length of illness and lesion etiology are shown in Table 1. Unilateral spatial neglect was assessed by the following three tests: Bells-test (Gauthier, Dehaut, & Joanette, 1989), line bisection and Draw-a-clock-face test (P. W. Halligan, J. Cockburn, & B.A. Wilson, 1991). Neglect was diagnosed if patients revealed impairments on at least two of three tests. Accordingly, patients were divided into three groups: Patients with signs of left-sided neglect (RBD+); patients without signs of neglect at testing, but with a previous neuropsychological diagnosis of neglect (RBD) and patients without signs of neglect and no previous history of neglect (RBD-) (see Table 2). The entire control group had no history of neurological disorders. There were no significant differences between the groups concerning age (Kruskal-Wallis-test: $\chi^2(3) = 1.25$, $p = 0.74$) and time since lesion ($\chi^2(2) = 1.43$, $p = 0.49$).



a)



b)



c)

Figure 2 Lesion maps and overlays

Lesion maps and overlap (bottom of each group) for all patients plotted onto a normal template using MRICron software (Rorden & Brett, 2000). Affected areas (translucent gray) are plotted onto axial slices, with numbers indicating Z-coordinates in Talairach space. Highest lesion overlap is shown in light red, lowest overlap in dark red.

a) Patients with spatial neglect, RBD+; b) Patients without spatial neglect, RBD; c) Patients with previous signs of spatial neglect, RBD–

Table 1

Demographical and anatomical data for right brain damaged patients

Subject	Age (years)/ sex (f/m)	Etiology	Months since lesion (months)
RBD+			
1	66/f	MCA	4.5
2	60/m	MCA	3.5
3	61/m	MCA	1
4	58/m	MCA	12
5	70/m	MCA	1
6	79/f	BGI	2.5
Average (SD)	65.7 (\pm 7.9)		4.1 (\pm 4.1)
RBD			
7	71/f	MCA	3
8	74/m	MCA	2
9	60/f	TA	2
10	57/m	MCA	4.5
11	85/f	MCA	1
12	76/m	ICB	2.5
Average (SD)	70.5 (\pm 10.4)		2.5 (\pm 1.2)
RBD–			
13	69/f	BGI	1
14	61/m	BGI	1.5
15	73/m	MCA & TA	1
16	78/m	MCA	4
17	69/m	BGI & TB	3
18	63/m	MCA	1
Average (SD)	68.8 (\pm 6.3)		1.9 (\pm 1.3)
Control			
19	81/f		
20	84/f		
21	59/f		
22	65/m		
23	55/f		
24	55/m		
Average (SD)	66.5 (\pm 13.0)		

RBD+: right-brain damaged with neglect; RBD: right-brain damaged with previous history of neglect, RBD–: right-brain damaged without neglect; MCA=middle cerebral artery infarction; ICB=intracerebral bleeding; BGI=basal ganglia infarction; TA=thalamic infarct; TB=thalamic bleeding

Procedure

All tasks were administered in a single session with patients seated at a desk.

Basic screening

Screening was administered before the actual experimental tasks to ensure basic cognitive abilities. The first part (A-D) of the Mini Mental Status Test (MMST) (Folstein, Folstein, & McHugh, 1975) was used to test subjects' orientation and memory. Individuals' identification of numbers, dates and elementary arithmetic skills were tested using the Aiblinger Acalculia Screening (AAT) (Keller & Maser, 2004). There were no significant differences between the four groups concerning MMST (Kruskal-Wallis-test: $\chi^2(3) = 0.77$, $p = 0.86$) and AAT scores (all $p > 0.05$). Results and group averages are displayed in Table 2.

Table 2

Basic screening and neglect assessment data

Subject	Group	MMST subtest A- D (21)	Number (3)	Date (3)	Calculation (3)	Line bisection (0/1)	Bell-test (0/1)	Clock- face (0/1)
1	RBD+	20	3	3	3	1	0	0
2	RBD+	21	3	3	3	0	0	0
3	RBD+	21	3	3	3	0	0	0
4	RBD+	14	0	0	0	0	0	0
5	RBD+	19	3	3	3	0	0	0
6	RBD+	14	3	3	0	0	0	0
Average (SD)		18.1 (± 3.3)	2.5	2.5	2	0.16	0	0
7	RBD	21	3	3	3	1	1	0
8	RBD	21	3	3	3	0	1	1
9	RBD	15	3	3	2	1	1	0
10	RBD	21	3	3	3	1	0	0
11	RBD	19	3	3	3	1	1	0
12	RBD	20	3	3	3	1	1	1
Average (SD)		19.5 (± 2.3)	3	3	2.8	0.83	0.83	0.33
13	RBD–	21	3	3	3	1	1	1
14	RBD–	20	3	3	3	1	1	0
15	RBD–	20	3	3	3	1	1	1
16	RBD–	19	3	3	3	1	1	0
17	RBD–	20	3	3	3	1	1	1
18	RBD–	20	3	3	3	1	1	1
Average (SD)		20 (± 0.6)	3	3	3	1	1	0.6

RBD–: right-brain damaged without neglect; RBD: right-brain damaged with previous history of neglect, RBD+: right-brain damaged with neglect;

Maximum scores are included in parentheses; Neglect assessment: 0 = impaired, 1 = normal

Time processing task

Subjects performed a time estimation and time bisection task. Subjects were seated at a distance of approximately 50 cm from a 15" screen. In the estimation condition, a green square was presented at the center of a white screen for a variable duration (encoding phase): 6 s, 12 s or 24 s. Immediately after the encoding phase, subjects were asked to verbally estimate how long the stimulus was presented for. Then, another green square with the same size and position appeared on the screen. Subjects were instructed to say "Stop" when they thought that half of the previously presented time interval (encoding phase) had elapsed. The "Stop"-signal triggered the end of the trial, response times were recorded and the square disappeared. This time bisection task is the temporal analogue of the spatial line bisection task. Subjects were explicitly instructed not to use any kind of strategy such as counting aloud, counting sub-vocally or looking at their watch. No accuracy feedback was given. Each duration was presented three times. The order of stimuli durations was randomized. Deviations between the reported and actual time on each trial were calculated by subtracting the two values, such that for time estimation negative values represent an estimated shorter time interval than the presented one, whereas positive values represent an estimated longer time interval than presented. For time bisection, negative values indicate that subjects bisected earlier in time than the true midpoint, whereas positive values indicate that they bisected later than the true midpoint. Deviations for both time estimation and bisection were averaged across trials separately for each stimulus duration.

Data analysis

Data analyses were computed with SPSS. We used non-parametric tests with an alpha level of 0.05. Differences in mean aberrations across time intervals were tested separately for each group with Friedman-Tests. In case of significant results, subsequent simple comparisons were conducted with two-tailed Wilcoxon-tests. Differences between the groups were tested separately for each interval length (for both tasks) with Kruskal-Wallis-tests. In case of significant results, subsequent paired comparisons were performed with two-tailed Mann-Whitney U tests. Due to a priori hypotheses based on previous, unpublished observations, no correction methods were applied.

2.1.3 Results

Within-group differences

Time estimation

Significant differences between time intervals were only found in the RBD+ group ($\chi^2 (2) = 12.0$, $p = 0.002$). Paired comparisons with Wilcoxon-tests indicated overestimations for the short interval (mean: +3 s), slight underestimations for the medium interval (mean: -1.44 s) and great underestimations for the long interval (mean: -9.28 s). All comparisons were found to be significant (all $p \leq 0.028$). The analysis for the RBD group yielded a trend for differences between time intervals ($\chi^2 (2) = 5.33$, $p = 0.069$). The pattern of estimation was the same as for the RBD+ group: overestimations (mean: +3.28 s) were found for the short interval, almost no aberration for the medium (mean: +0.72 s) and underestimations (mean: -7.0 s) for the long interval. No significant differences across time intervals were found in the RBD- group ($\chi^2 (2) = 3.0$, $p = 0.22$) or in the control group ($\chi^2 (2) = 2.33$, $p > 0.05$).

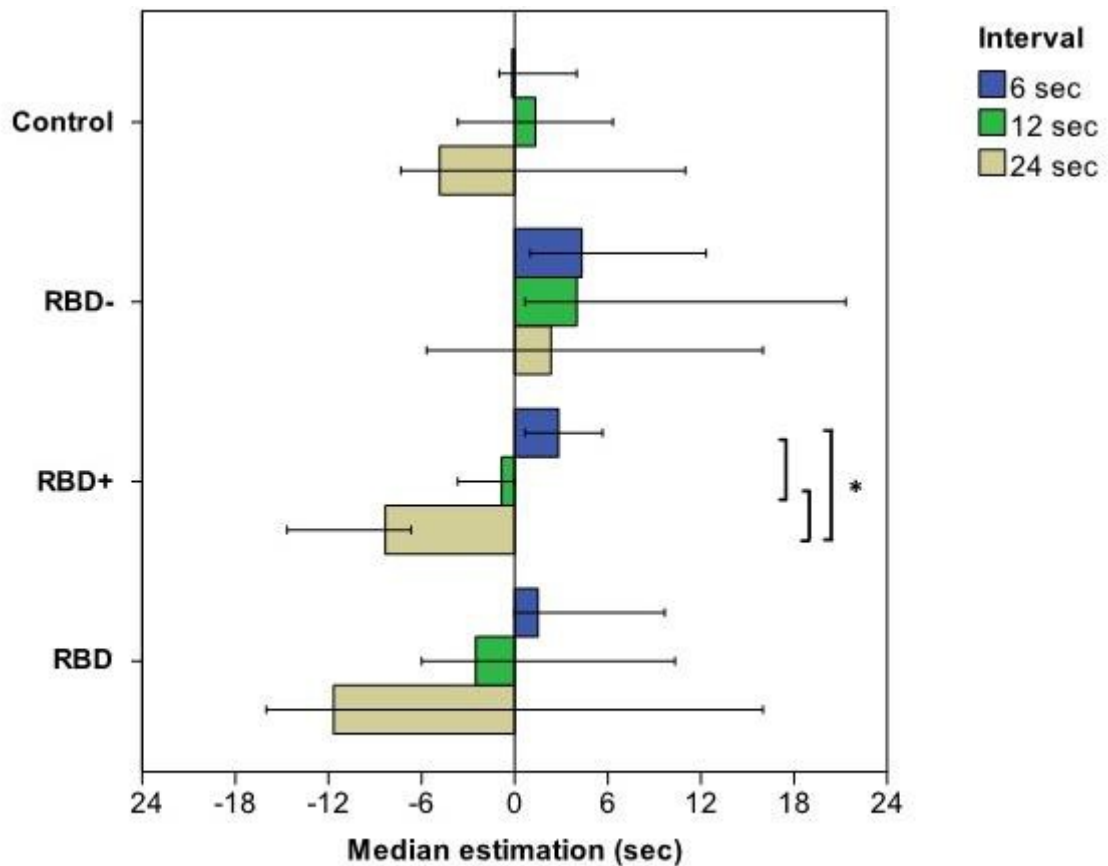


Figure 3 Time estimation in all groups.

Median aberrations in seconds and 95 % confidence interval of time interval length and groups are displayed. * $p < 0.05$ (paired Wilcoxon-tests)

Time bisection

Significant differences between time intervals were found for both the RBD+ ($\chi^2(2) = 12.0$, $p = 0.002$) and the RBD group ($\chi^2(2) = 9.33$, $p = 0.009$). In the RBD+ group all subsequent paired comparisons yielded significant results (all: $Z = -2.20$, $p \leq 0.028$). Bisections forward in time decreased from the short (mean: +3.38 s) to the medium (mean: +2.05 s) interval, and turned into bisections earlier in time for the long interval (mean: -3.22 s). A similar pattern was observed for the RBD group: bisections forward in time for the short (mean: +1.45 s), almost no aberration for the medium (mean: +0.66 s) and bisections earlier in time for the long interval (mean: -4.71 s). However, only the comparisons between the short and long as well as the medium and long interval reached statistical significance (both $Z = -2.20$, $p = 0.028$). No differences across time

intervals were found for the RBD– group ($\chi^2 (2) = 4.0, p \geq 0.05$). For the control group the same pattern as in the RBD+ and RBD group was found, however less pronounced: bisections forward in time for the short (mean: + 0.9 s), changed to a smaller aberration for the medium (mean: + 0.5 s) and bisections slightly earlier in time for the long interval (mean: -1.1s) ($\chi^2 (2) = 8.09, p = 0.018$). Paired comparisons showed significant results between the short and long and the medium and long interval ($Z = -2.02, p = 0.043$ and $Z = -2.02, p = 0.028$ respectively).

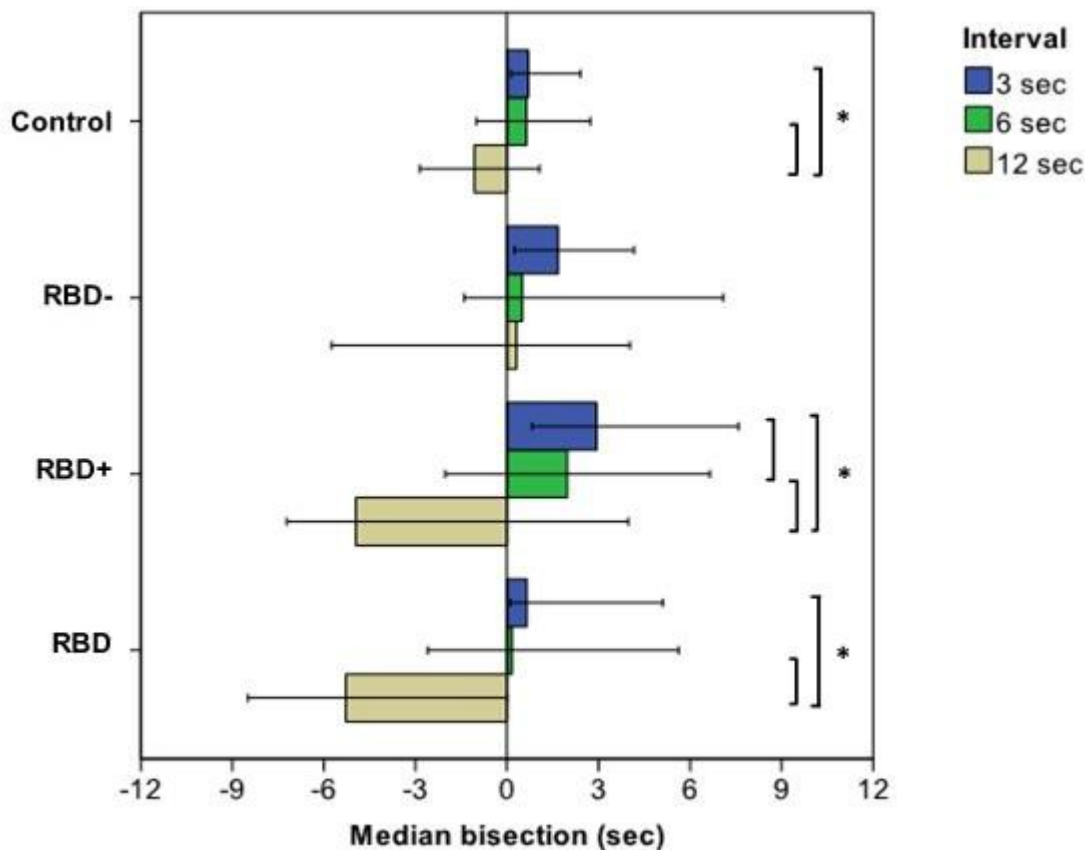


Figure 4 Time bisection in all groups.

Median aberrations in seconds and 95% confidence intervals of time interval length and groups are displayed. * $p < 0.05$ (paired Wilcoxon-tests)

Between-group differences

Time estimation

Significant differences between groups were found for the long time interval ($\chi^2(3) = 10.79, p = 0.013$). Post-hoc comparisons yielded significant differences between the control and RBD+ group ($Z = -2.57, p = 0.010$), RBD+ patients' underestimations deviated significantly greater than those of controls (-9.28 s vs. -3s respectively).

Time bisection

No significant differences between the groups were found for any of the time intervals ($p > 0.05$ for all comparisons).

Regression line slopes

Due to the prominent pattern of over- and underestimations in the RBD+ and RBD patients and the striking difference to the RBD- group, we were interested in two points: firstly, if there was a statistically significant regression towards the mean for any of the groups and secondly, if there were significant differences between the groups. The regression coefficients were calculated for each patient and task in logarithmic space, and additional analyses (Kruskal-Wallis test, and post-hoc Mann-Whitney U tests) compared these between the four groups. Post-hoc analyses compared the control group with all other groups, and the two groups with spatial deficits. Multiple comparisons were corrected with the Bonferroni method.

There were significant differences between the groups for the estimation task ($\chi^2(3) = 11.91, p < 0.01$). Post-hoc analyses revealed significant differences between the control (-3.7) and the RBD (-20.4) group ($Z = -2.88, p < 0.0125$) (Fig.5).

There were also significant differences in regression coefficients for the bisection task ($\chi^2(3) = 12.85, p < 0.01$). Post-hoc analyses revealed significant differences between the control (-3.4) and the RBD (-10.9) group ($Z = -2.88, p < 0.0125$) and between the RBD- and RBD group ($Z = -2.81, p < 0.0125$) (Fig. 6).

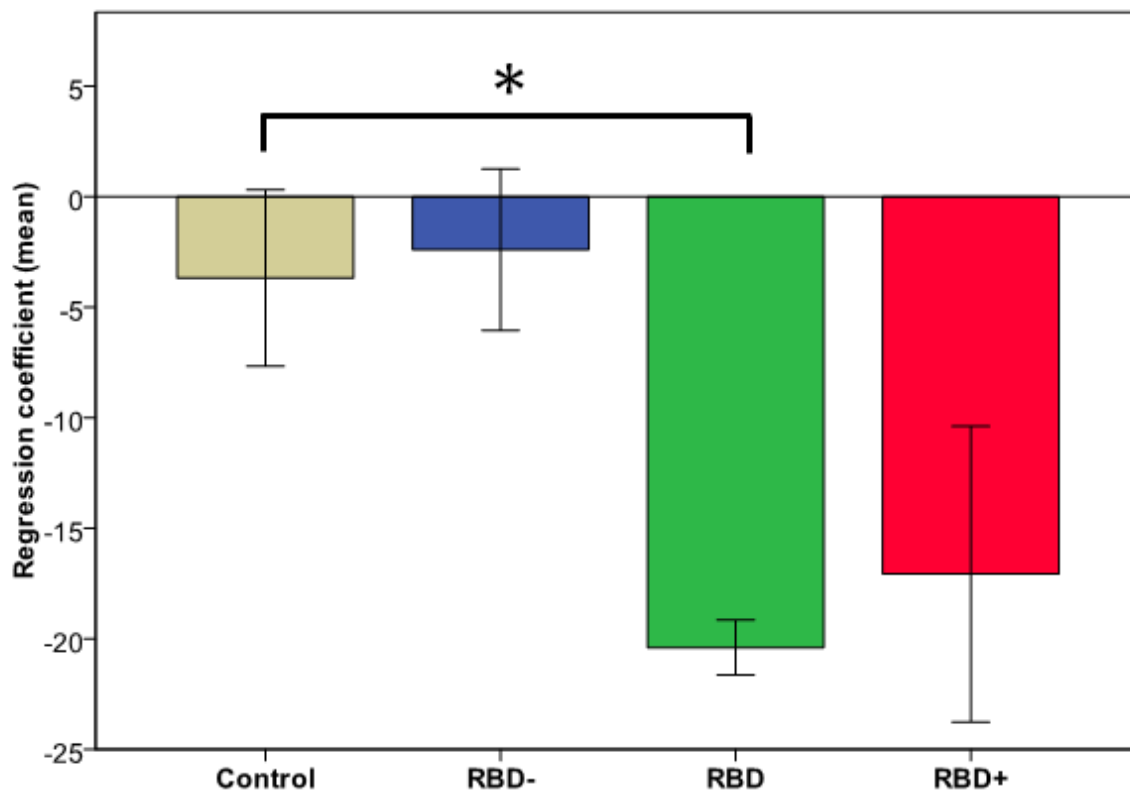


Figure 5 Regression coefficients for the time estimation task

The regression coefficients (mean \pm standard error) for all groups in the time estimation task. Greater values indicate a stronger regression to the mean. * $p < 0.0125$ (Wilcoxon tests)

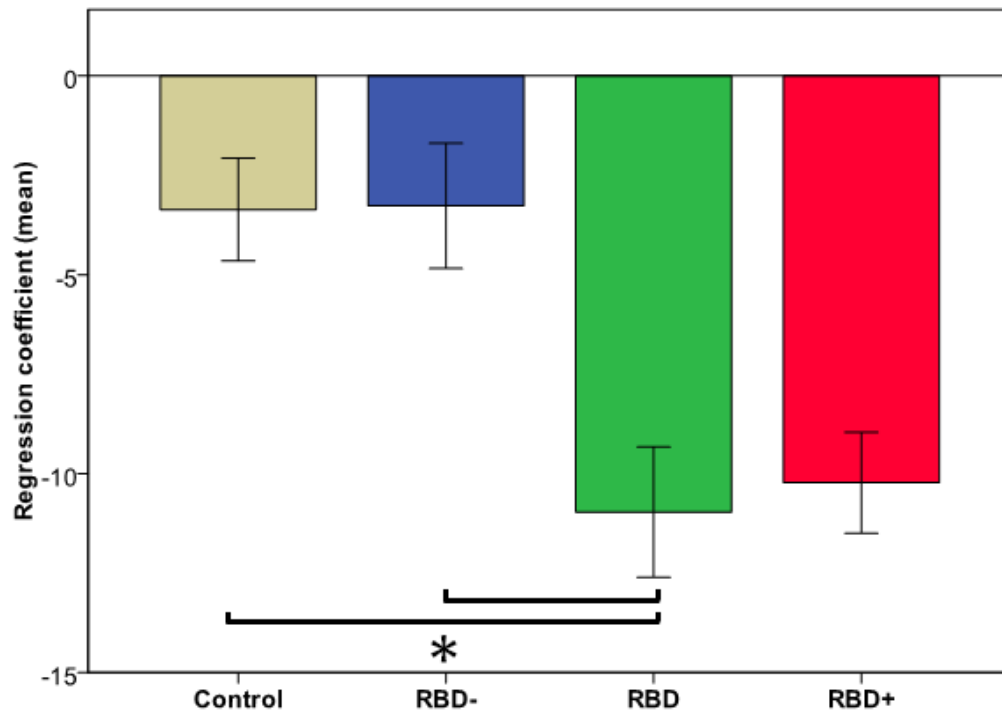


Figure 6 Regression coefficients for the time bisection task

The regression coefficients (mean \pm standard error) for all groups in the time estimation task. Greater values indicate a stronger regression to the mean. * $p < 0.0125$ (Wilcoxon tests)

2.1.4 Discussion

The aims of the present study were to investigate multi-second time estimation and bisection in right brain-damaged patients, and the influence of spatial deficits – current and previous – on time processing.

Time estimation

Both the RBD+ and the RBD group showed an estimation pattern that varied across different interval lengths: short intervals were overestimated, long intervals underestimated, and medium intervals were estimated quite accurately. The largest deviations were evident in RBD+ patients. In contrast, RBD- patients generally

overestimated time intervals across all durations. Healthy controls showed only minimal aberrations from the correct duration.

These findings support the notion that right brain-damaged patients both with and without spatial deficits are impaired on time processing tasks (Danckert et al., 2007). For time estimation in the range of 5-60s, Danckert et al. (2007) also found impairments for right brain-damaged patients both with and without neglect. Time estimations of both patient groups were modulated by time interval length, in that they increased with increasing interval length. However, Danckert et al. (2007) found underestimations for both patient groups across all time intervals, while we found distinctions between patients with and without spatial deficits. We only found modulations of time estimation by interval length for patients with spatial deficits. Those without spatial deficits overestimated across all interval lengths. As mentioned above, these discrepancies between Danckert et al.'s (2007) and our findings might be due to differences in stimulus material: We used stationary squares, while Danckert et al. (Danckert et al., 2007) used illusory motion stimuli with a simultaneous number counting task. Even though the authors report that they checked the influence of numbers and motion speed in pilot tests on healthy controls, both of these factors might still have influenced patients' estimations. Several studies have shown an influence of numbers on temporal processing (Brown, 1997; Cappelletti et al., 2009; Dormal et al., 2006; Oliveri et al., 2008). Thus, based on our findings, we conclude that neglect patients do not generally underestimate time intervals. Estimations seem to be dependent on the stimulus material.

The distinct estimation patterns that we found for the different groups were associated with differences in regression to the mean. While RBD+ and RBD patients exhibited regression to the mean, the RBD- group did not show this effect. Regression to the mean is observed in many psychophysical magnitude estimation experiments and is also referred to as Vierodt's Law (Lejeune & Wearden, 2009): values close to the center of the stimulus range are estimated quite accurately while lower values are over- and higher ones are underestimated (Stevens & Greenbaum, 1966; Teghtsoonian & Teghtsoonian, 1978). Regression to the mean is assumed to result from a statistical combination of subjects' previous experience and an implicit knowledge about the uncertainty of a measurement (Laming, 1999). Recent modeling studies have confirmed this assumption for time reproduction (Jazayeri & Shadlen, 2010). RBD+ and RBD patients' prominent regression to the mean could thus either stem from a stronger reliance on previous

experience or a higher degree of uncertainty about a measurement. As RBD– patients lacked any modulation across different intervals, they seemed to be unable to encode the input. However further studies are needed to confirm these hypotheses.

Time bisection

On the time bisection task, RBD+, RBD and healthy subjects bisected later in time for short and medium intervals, and bisected earlier in time for long intervals. This pattern was most pronounced for RBD+ patients. RBD– patients also bisected later in time for the short and medium interval; but were quite accurate for the long interval.

For time intervals of 6 and 12s, our findings are in line with other studies using similar stimulus material in the range of 1.6-2.4s (Frassinetti et al., 2009; Magnani et al., 2011; Oliveri et al., 2009; Oliveri et al., 2013). They reported that neglect patients bisected time intervals later in time than the true midpoint and concluded that time passed by slower for these patients. For the 24s interval, however, our patients with current and previous spatial deficits bisected earlier in time compared to the true midpoint. This could indicate that time is perceived as passing by faster on longer time scales or that the interval exceeded patients' attentional span and was thus perceived as shorter. Future studies also investigating patients' attentional capacities and additional time intervals would however be needed to distinguish between these possibilities.

Unlike the studies by Oliveri et al. (2009; 2013), we also observed impairments on the time bisection task for right brain-damaged patients without spatial deficits. While our patients tended to bisect later than the true midpoint on the 6 and 12s interval, Oliveri et al. (2009; 2013) reported accurate bisections for 1.6-2.4s intervals. One reason for these discrepancies may be that in the study conducted by Oliveri et al.'s (2009; 2013) patients received a time estimation training before the experimental task.

Spatial impairments and lesion locations

All patients with current and previous spatial impairments exhibited similar deviation patterns on both time estimation and bisection, which were modulated by time interval length. Interestingly, RBD patients who compensated their spatial deficits in everyday life, were still impaired on temporal processing. This suggest that performance on our spatial and time tasks is either not supported by the same processes or that the association between the two is not very strong. Consistent with a distinct mechanisms

for temporal processing, patients with intact spatial processing (RBD–) were also impaired, however in a different manner, on both time tasks. They were rather unable to encode time intervals than disturbed in their magnitude estimation. Thus, the actual encoding of time intervals seems to be separate from a multi-dimensional magnitude center. It has to be noted though that our experiments were not primarily designed for identifying processing pathways. The aforementioned interpretations are thus speculative and need further investigation to be confirmed.

Interestingly, the behavioral differences between patient groups seem to be associated with differences in lesion locations. RBD+ and RBD patients both suffered from extended cortical lesions in frontal and parietal areas (Fig. 2). Right parietal areas are highly involved in temporal processing (Bueti & Walsh, 2009): the maintenance (Oliveri et al., 2009; Rao, Mayer, & Harrington, 2001) and reproduction of time intervals (Coull, Davranche, Nazarian, & Vidal, 2013), and temporal-spatial processing (Koch, Oliveri, & Caltagirone, 2009). Connections from parietal to prefrontal areas are important for a conscious representation of temporal intervals (Koch et al., 2009). It is thus possible that the RBD+ and RBD patients were not able to pay proper attention to the temporal information, consciously represent the time interval, and/or maintain it until the end of the interval. In contrast, RBD– patients generally overestimated time intervals. These patients had lesions mainly in subcortical areas with about two-thirds exhibiting lesions in the basal ganglia and/or thalamus (Fig. 2). The basal ganglia are known to be strongly involved in time encoding (Koch, Oliveri, Torriero, & Caltagirone, 2003; Lewis & Miall, 2006; Nenadic et al., 2003), especially for supra-second time intervals (Koch et al., 2009). Presumably, RBD– patients had difficulties encoding the length of time intervals. This would completely disrupt any magnitude estimation behavior, so that estimations are not correlated with interval lengths.

A possible limitation to these findings are the differences between groups in overall lesion size. Another possibility for future investigations would be voxel-based lesion symptom mapping. We did not apply it for this sample due to the small sample size and the limited amount of observational data.

Overall, some limitations of our study have to be considered: we cannot exclude the possibility of subjects using sub-vocal counting strategies to solve the task. We would however expect better results if that was the case. Moreover, patients with right brain-damage typically have a lowered attention span (Corbetta & Shulman, 2011) which might

have influenced the present results. Overall, the limited number of trials decreases the explanatory power of our results.

2.1.5 Conclusions

Our results indicate that right brain-damaged patients are impaired on time estimation and bisection in the multi-second range. Temporal deficits of patients without spatial deficits were distinct from those of patients with current or previous spatial deficits. Indicating an association between time and space, all patients with spatial deficits (current and previous) were impaired on temporal processing. However, the compensation of spatial deficits over the course of rehabilitation did not entail improvements of temporal deficits. This indicates either partly distinct processing routes of time and space or that the association between the two is not very close. Additional research is needed to further explore the association between time and space.

2.2 Verticality perception during and after galvanic vestibular stimulation

2.2.1 Introduction

Humans construct and update their sense of verticality by integrating vestibular, somatosensory, and visual input (Barra et al., 2010). The different sources of sensory information are processed by partially overlapping, but largely independent neural networks (Baier, Suchan, Karnath, & Dieterich, 2012; Barra et al., 2010; G. Bottini et al., 2001). The internal estimate of verticality can be assessed by different methods, testing preferentially the vestibular-visual, the tactile and the postural modalities (subjective visual, haptic, and postural vertical). It has been shown that these modalities can be differentially affected in patients with impaired spatial orientation or balance control (Karnath & Dieterich, 2006; D. A. Perennou et al., 2008).

Transmastoidal GVS acts on afferents from the otoliths and the semicircular canals. It was shown to affect subjects' perception of verticality. During stimulation the subjective visual (SVV) and the subjective haptic vertical (SHV) deviate towards the anode (Lenggenhager et al., 2008; Mars, Popov, & Vercher, 2001; Mars, Vercher, & Popov, 2005; Saj, Honore, Bernati, et al., 2005). GVS also causes eye torsion and nystagmus via the vestibular-ocular reflex (Jahn et al., 2003) and – with the head upright - body tilt towards the anode via vestibulo-spinal reflexes (Wardman, Taylor, et al., 2003). Recently, GVS was used as a therapeutic tool to improve balance and spatial orientation in stroke patients (Krewer et al., 2013; Saj et al., 2006).

However, existing studies on verticality perception have only examined the online effects of GVS, since judgments of verticality were always generated *during* stimulation intervals. In the oculomotor domain, GVS is known though to elicit reverse responses after it is switched off: eye rotations and nystagmus towards the cathode. Depending on stimulation duration, these responses even lasted up to 6 min (H.G. MacDougall et al., 2002; H. G. MacDougall et al., 2003). Such aftereffects were the reverse of the response *during* stimulation in which GVS-induced eye movements were directed towards the anode (Severac Cauquil et al., 2003; Watson et al., 1998; Zink et al., 1998). It is not known if these aftereffects exist for the subjective verticals and whether there are any differences between modalities. This is of relevance since the time course and magnitude of effects and aftereffects of GVS on verticality perception might influence

responses to therapeutic interventions. Thus, the purpose of this study was to examine the influence of GVS on different subjective verticals (visual, haptic, and postural) both during and after its application.

2.2.2 Material and Methods

Galvanic vestibular stimulation

Bilateral bipolar GVS was delivered by a battery-driven, direct current stimulator (neuroConn Ilmenau, Germany). Electrodes were covered with sodium-chloride soaked sponges (30 cm² each). Current was ramped up (in steps of 0.1 mA/sec) to 1.5 mA and turned off at the end of the stimulation period.

Assessment of verticality perception

Subjective Visual Vertical (SVV)

The SVV was assessed with the so-called bucket test. The seated subjects indicated when they visually perceived a dark line (13cm long, 0.3cm wide, at 23cm distance) as being vertical. SVV assessments with the bucket test exhibit good inter- and intra-test reliability (Zwergal et al., 2009b).

Subjective Haptic Vertical (SHV)

The SHV was measured with a rod (27 cm long, 1 cm wide) mounted onto a vertical plate 40cm in front of the subject (for a similar device see Funk, Finke, Muller, Preger, et al., 2010). While seated and blindfolded, the subjects' task was to adjust the wooden rod, with their right hand using a precision grip until they perceived it to be in a vertical position. To prevent them receiving any reference cues, they were not allowed to touch the device's plate or the desk. A scale was mounted onto the plate to record subjective vertical adjustments.

Subjective Postural Vertical (SPV)

The SPV was measured in the Spacecurl, a cardanic suspension apparatus that consists of three concentric rings. The blindfolded subject stood in the centre of the apparatus on a platform that was attached to the midmost ring. The device was tilted in the frontal plane, and subjects had to indicate when they felt they were in an upright position. The SPV measurements in the Spacecurl show good test-retest and intra-rater reliability in healthy subjects (unpublished results).

Six adjustments per trial were performed in randomized order of starting positions (for SPV 12°, 15° & 18°; for SVV and SHV 15°, 25° & 40°). Half of the trials started from a clockwise, half from a counter-clockwise position. The six adjustments were averaged for each trial and modality to calculate the SPV, SVV, and SHV. Data were normalized so that positive values indicated deviations from the earth vertical to the side of the anode, and negative values, deviations in the direction of the cathode.

Experiments

The Ethics Committee of the Ludwig-Maximilians-University Munich approved this study (Number 405-11). All subjects provided their written informed consent.

Exp.1 Manipulation of subjective verticals

To investigate online effects and aftereffects of GVS on verticality perception across different modalities, ten healthy subjects and eight right brain-damaged patients participated in experiment 1 (see Table 3 for demographic and clinical data). All patients were tested for spatial neglect using the Mesulam test, line bisection and the draw-a-clockface test. Patients were classified to have neglect if they were diagnosed with neglect in at least two of the three tests. Furthermore, somatosensory deficits were assessed with the somatosensory score of the Fugl-Meyer assessment for lower extremity.

All subjects performed the SPV, the SVV, and the SHV immediately before (baseline), during, and 3 minutes after a period of GVS. The experiment was conducted on two

consecutive days with a fixed sequential order: the SPV on day 1, the SVV and SHV on day 2. The polarity of the GVS current was varied between subjects. Stimulation was applied for the duration of verticality adjustments (4-8 minutes).

Table 3

Demographic and clinical patient data.

Patient	Etiology	Time since lesion (months)	Age (years)	Gender	Neglect	Somatosensory deficit	SVV (°)	SHV (°)	SPV (°)
1	MCA	1.4	77	m	y	y	1.5	-1.3	0.8
2	MCA	2.8	51	m	n	y	-2.3	-3.8	-0.4
3	MCA	1.5	74	m	y	y	1.0	-2.2	-0.4
4	MCA	2.7	57	m	y	y	0.0	2.6	4.8
5	MCA	1.7	72	m	y	y	5.2	4.7	0.7
6	MCA	3.4	59	m	n	n	2.8	-0.8	-0.6
7	MCA	0.7	71	m	n	n	-0.7	1.6	1.0
8	MCA	1.7	68	m	y	n	-3.7	-2.2	2.5
Patient (Mean ± SD)		2.0 ± 0.9	66 ± 9	8 m			0.5 ± 2.8	-0.2 ± 2.8	1.1 ± 1.8
Healthy (Mean ± SD)			59 ± 6	5 m/5 f			0.8 ± 1.5	0.6 ± 1.9	0.6 ± 1.4

MCA = middle cerebral artery infarction; m = male, f = female; y = yes, n = no

Exp. 2 Time course

A second experiment was designed to determine the time course of online effects and aftereffects of GVS on verticality perception. Since the haptic modality was most responsive to GVS, the time course was studied for the SHV. Fourteen young healthy subjects (mean age: 34 years, SD: ± 6.15 ; 7 females) were tested in experiment 2. The subjects repeatedly performed the SHV during and after a 20-minute period of GVS. All subjects were stimulated with the cathode over the left and the anode over the right mastoid. The SHV was assessed immediately before starting GVS (baseline), 0.5, 5, 10, 15, and 20 minutes after starting the stimulation (trials 1 - 5) and at the same time points after terminating GVS (trials 6 - 10).

Data analysis

A repeated-measures ANOVA with one within-subject factor (modality) and one between-subject factor (group) was used to evaluate differences between groups and modalities at baseline. To determine any differences in verticality adjustments across time points (baseline, during, after GVS), modalities (SVV, SHV, SPV), and groups (healthy subjects, patients) a factorial repeated-measures ANOVA was performed with two within-subject factors (time and modality) and one between-subject factor (group). Another factorial repeated-measures ANOVA (within-subjects factors modality and type of effect, between-subject factor group) was conducted to compare the magnitudes of online effects and aftereffects across modalities. Effect magnitudes were calculated as absolute differences between baseline and during GVS (online effect) and during and after GVS (aftereffect). In case of significant results subsequent multiple comparisons were performed and Bonferroni corrected.

For experiment 2 differences across trials were analyzed using a one-way repeated-measures ANOVA and subsequent repeated contrasts. Verticality adjustments during (trials 1-5) and after GVS (trials 6-10) were grouped and compared using a paired t-test. The data were analyzed with SPSS Statistics 17.0. The significance level for α was set at 0.05.

2.2.3 Results

Exp.1 Manipulation of subjective verticals

There was no significant effect of modality ($F(2,32)=0.463$, $p=0.633$) or group ($F(1,16)=0.073$, $p=0.790$) for the baseline values.

The factorial repeated-measures ANOVA across all time points, showed a significant main effect of time ($F(1.49,23.84)=17.283$, $p<0.001$), but not of modality ($F(2,32)=0.065$, $p=0.837$) nor group ($F(1,16)=0.744$, $p=0.401$). Post-hoc tests revealed significant differences between the adjustments before and during GVS ($p=0.007$) and during and after GVS ($p<0.001$). There was a significant interaction between time and modality ($F(4,64)=5.214$, $p=0.001$): Differences between adjustments before and during GVS were smaller for the SPV than for the SVV and SHV; adjustments during and after GVS were also smaller for the SPV than for the SHV. Analysis of the effect magnitudes showed a significant main effect of modality ($F(1.32,21.15)=12.515$, $p=0.001$), a trend for the effect type ($F(1,16)=4.111$, $p=0.060$), but no effect of group ($F(1,16)=0.652$, $p=0.431$) and no significant interaction ($F(2,32)=0.359$, $p=0.701$). Post-hoc test revealed significantly greater online effects and aftereffects for the SHV than for the SVV ($p=0.010$) and the SPV ($p>0.001$). Furthermore, the aftereffect tended to be greater than the online effect across all modalities. Normalized verticality adjustments during and after stimulation are shown in Fig.7 for healthy subjects and in Fig.8 for patients.

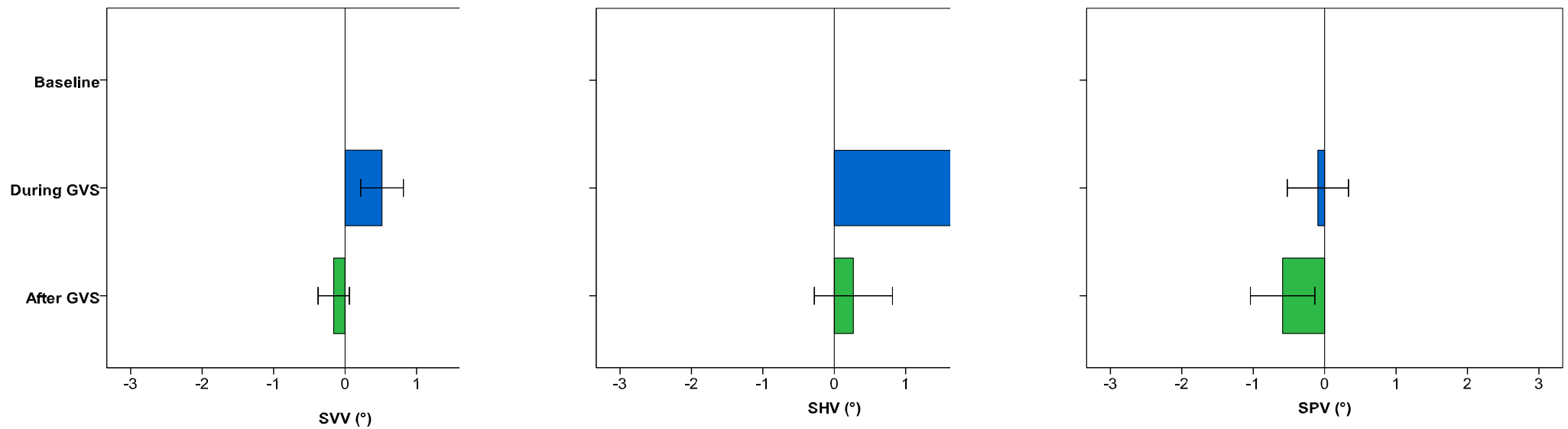


Figure 7 GVS in healthy subjects.

Adjustments (mean \pm standard error, normalized to baseline and side of anode) of the subjective verticals during and after galvanic vestibular stimulation for healthy subjects. Positive values indicate a tilt to the side of the anode, negative values a tilt to the side of the cathode. SVV, subjective visual vertical; SHV, subjective haptic vertical, SPV, subjective postural vertical; GVS, galvanic vestibular stimulation.

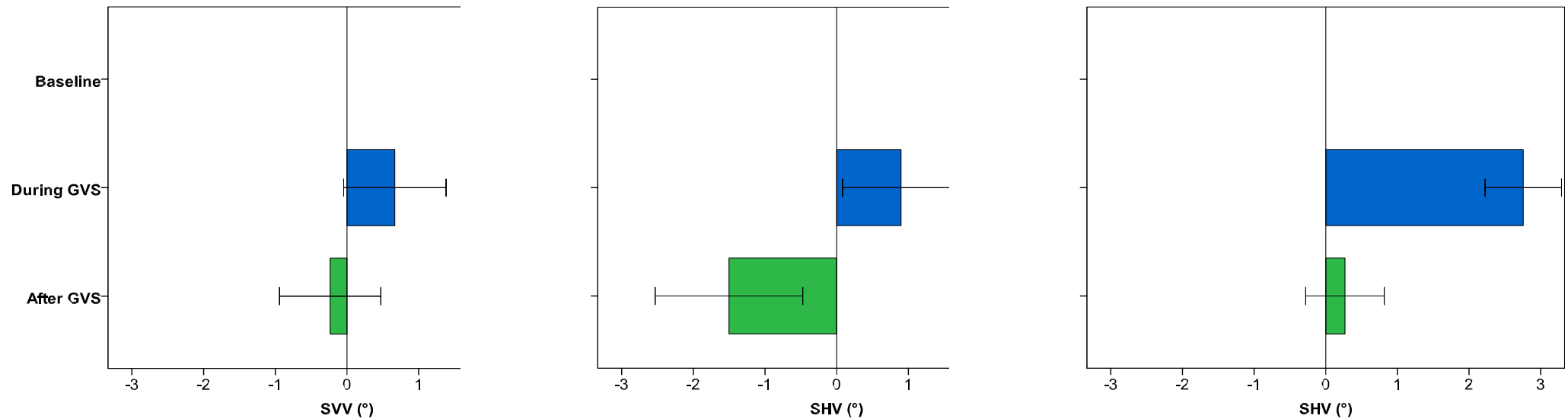


Figure 8 GVS in spatial neglect.

Adjustments (mean \pm standard error, normalized to baseline and side of anode) of the subjective verticals during and after galvanic vestibular stimulation for neglect patients. Positive values indicate a tilt to the side of the anode, negative values a tilt to the side of the cathode. SVV, subjective visual vertical; SHV, subjective haptic vertical, SPV, subjective postural vertical; GVS, galvanic vestibular stimulation.

Exp.2 Time course

The average SHV at baseline was $-0.6 \pm 2.9^\circ$. There were significant differences between trials ($F(10,130)=2.241$, $p=0.019$). Contrasts revealed differences between baseline and trial 1 ($F=7.279$, $p=0.018$), trials 5 and 6 ($F=10.852$, $p=0.005$), and trials 9 and 10 ($F=8.779$, $p=0.011$) (Fig. 2). Accordingly, the SHV changed when turning stimulation on and off, and the latter effect had decayed after 20 minutes. Trials 1 and 2 ($F=4.539$, $p=0.053$), and trials 4 and 5 ($F=3.557$, $p=0.082$) tended to be different. The SHV adjustments during GVS (trials 1-5) differed significantly from the adjustments after stimulation (trials 6-10) ($T(69)=4.398$, $p<0.001$).

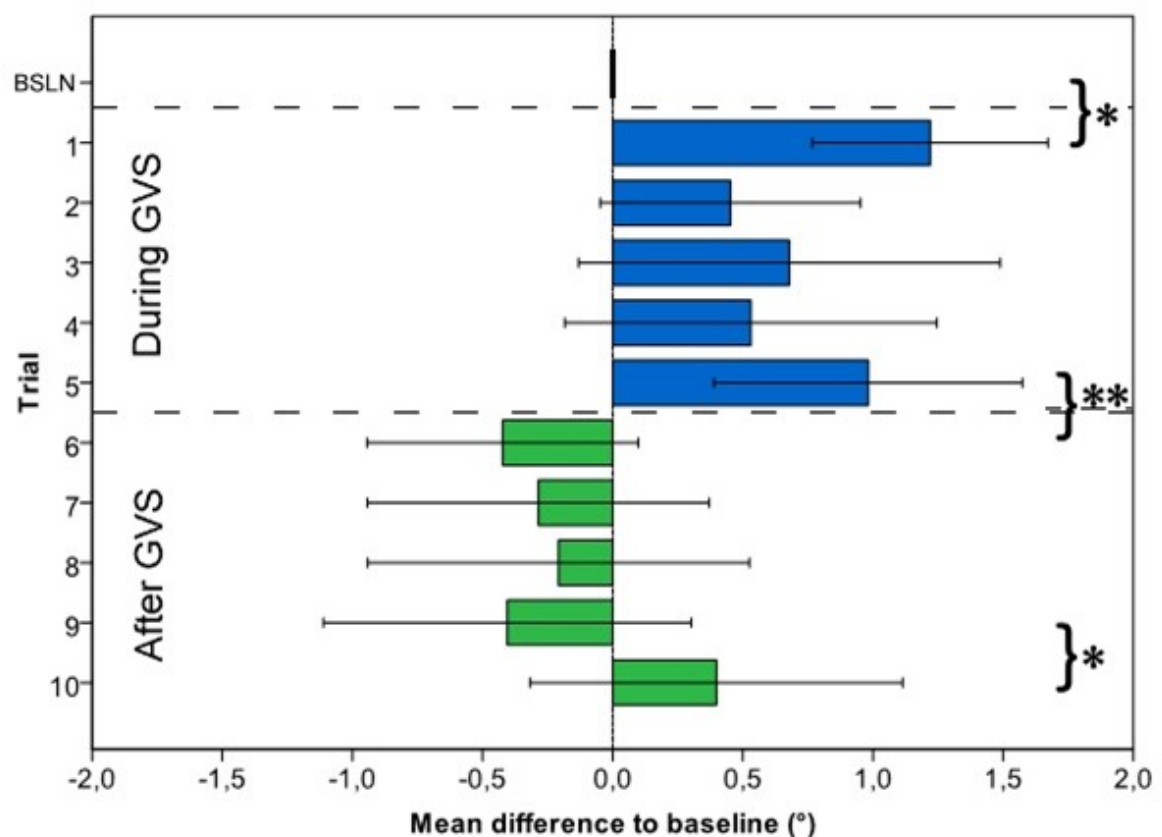


Figure 9 Time course of GVS effects.

Time course of haptic verticality adjustments (mean \pm standard error, normalized to baseline) during and after 20 minutes of galvanic vestibular stimulation. Times of assessment were 0.5, 5, 10, 15, and 20 minutes into stimulation (trials 1-5) and at the same time points after stimulation (trials 6-10). Positive values indicate a tilt to the side of the anode, negative values a tilt to the side of the cathode. BSLN, baseline; GVS, galvanic vestibular stimulation; SHV, subjective haptic vertical. Contrasts: * $p < 0.05$, ** $p < 0.01$.

2.2.4 Discussion

Our results provide the first direct evidence for the presence and time course of both online effects *and* aftereffects of GVS on the subjective verticals across different modalities.

Manipulation of subjective verticals

During stimulation healthy subjects' SVV and SHV – but not SPV – shifted towards the anode. The shift was strongest for the haptic modality. After stimulation was switched off, this effect reversed across all three modalities, with an overshoot towards the cathode. The only condition showing no overshoot, was the SHV in healthy subjects.

Anodal shifts during GVS are consistent with previous findings (Mars et al., 2001; Saj et al., 2006; Wardman, Taylor, et al., 2003) showing that verticality perception can be influenced by manipulating the vestibular input. Former studies demonstrated the SVV to be more malleable by GVS than the SHV, but we found the opposite to be the case (Mars et al., 2001; Wardman, Taylor, et al., 2003). This might be due to differences in experimental protocols causing different degrees of ocular torsion. GVS-induced ocular torsion is known to influence the SVV (Zink et al., 1998), but also to decline over time (H.G. MacDougall et al., 2002). While in previous experiments current was applied individually for each trial with SVV adjustments time-locked to current onset, we stimulated continuously across trials. Thus, GVS-induced ocular torsion was presumably reduced in our measurements compared to recordings at stimulus onset, resulting in less pronounced effects of GVS on the SVV.

For the SHV ocular torsion appears to be rather negligible (Bronstein, Perennou, Guerraz, Playford, & Rudge, 2003). The SHV is known to be influenced by somatosensory input: proprioceptive and tactile cues from the hand, arm and shoulder, as well as the trunk (Fourre et al., 2009) and neck (Guerraz, Luyat, Poquin, & Ohlmann, 2000) are known to exert considerable influence on SHV performance. Findings on the role of the vestibular system are mixed. While the SHV of two patients with unilateral vestibular nuclear lesions was only marginally affected (Bronstein et al., 2003), a study with healthy controls indicated a major role of the vestibular system in SHV adjustments (Schuler, Bockisch, Straumann, & Tarnutzer, 2010). Our results support this crucial role

of the vestibular system: subjects' SHV adjustments were strongly altered when manipulating the vestibular system with GVS.

In contrast to the SVV and SHV, we found no significant modulation of the SPV during GVS. Similarly, Bisdorff, Wolsley, Anastasopoulos, Bronstein, and Gresty (1996) reported no effect of GVS on the SPV; however, they observed a broader range, within which subjects felt vertical during stimulation. One possible explanation for these findings might be that verticality is processed by distinct pathways in different modalities and thus possibly affected differently by GVS (Karnath, Ferber, & Dichgans, 2000). Another explanation for the limited effect of GVS on the SPV might be the abundance of somatosensory information. Somatosensory information – if available – is known to be crucial and even sufficient for an accurate SPV estimation (Barra et al., 2010; Joassin, Bonniaud, Barra, Marquer, & Perennou, 2010; Mars et al., 2005). In our set-up, different tactile information was provided by the Spacecurl's padded restraints around hips and the pressure distribution under the feet. When sensory input from different sources is integrated, possible sensory conflict is resolved by weighting more reliable input stronger (Ernst & Bulthoff, 2004). Body tilts generate somatosensory asymmetries that improve the reliability of somatosensory input compared to symmetric signals in upright position (Bronstein & Guerraz, 1999; Mars et al., 2005). Consequently, the somatosensory input in our experiment was presumably considered more reliable for estimating the SPV than the conflicting vestibular input.

In contrast to these online effects, we found the reverse effect *after* stimulation: in all modalities the subjective vertical shifted towards the cathode. The aftereffects tended to be larger than the online effects resulting in an overshoot in the direction of the cathode after stimulation. In addition, effect magnitudes differed between modalities, in that both online effects and aftereffects were most pronounced for the haptic modality.

Aftereffects of GVS have also been reported for the oculomotor domain and body movements (H.G. MacDougall et al., 2002; H. G. MacDougall et al., 2003; St George et al., 2011; Tax et al., 2013). When GVS is turned off, ocular torsion and nystagmus reverse direction and are directed towards the cathode.

Studies investigating effects of GVS on body movement found a sway towards the anode during stimulation (Fitzpatrick & Day, 2004; Wardman, Taylor, et al., 2003), which reversed direction after stimulation. The magnitude of this aftereffect was significantly larger than the online effect (Tax et al., 2013). Similarly, GVS-induced perceptions of

rotation were also found to change direction after stimulation. Percepts during and after stimulation had similar peak magnitudes (St George et al., 2011).

While we found no differences between healthy subjects and right brain-damaged patients, Saj et al. (2006) reported stronger online effects of GVS on visuo-tactile verticality adjustments in right brain-damaged patients than in healthy subjects. The largest effects were found in patients with spatial neglect who typically show counter-clockwise SVV and SHV deviations (Kerkhoff, 1999). Since these deviations shifted towards the anode during GVS, Saj et al. (Saj et al., 2006) proposed that right anodal stimulation could alleviate neglect patients' spatial deficits. However, we found that online effects reversed after switching the stimulation off - with a slight overshoot towards the cathode. Since the time course of these aftereffects is the critical factor in terms of therapy, it was investigated in experiment 2.

Time course

For the SHV, we found that GVS-induced shifts lasted not only during stimulation; but also up to at least 15 minutes after stimulation. When stimulation started, subjects SHV showed an anodal shift that was strongest immediately after the onset of GVS. This shift persisted during the entire 20-minute stimulation interval. When stimulation was switched off, the SHV reversed direction and shifted towards the cathode. This effect persisted for at least 15 minutes after stimulation, but vanished somewhere between 15 and 20 minutes.

These findings are in line with studies on GVS-induced eye movements and movement perceptions. A 6-min time constant for the decay of reverse eye movement responses was reported for a 5-minute stimulation interval. Response strength was linearly related to current intensity (H. G. MacDougall et al., 2003). Similarly, rotation perceptions during and after stimulation had comparable peak magnitudes and time courses of decay (St George et al., 2011). GVS-induced aftereffects appear to be directly related to the stimulation interval. Until now, however, this has not been explicitly confirmed for the subjective verticals.

The longer-lasting reversed tilts of the subjective verticals that occurred after the application of GVS reflect adaptive mechanisms during prolonged stimulation. This may have important implications for the use of GVS in the rehabilitation of distorted verticality

perception. Based on earlier studies, GVS was proposed as a therapy for pusher behavior and spatial neglect (Krewer et al., 2013; Saj et al., 2006). Evidence on its effectiveness, however, is lacking. The placement of the electrodes for therapy has so far been based on the effects observed during stimulation. Thus, neglect patients' counter-clockwise verticality deviations were ameliorated when the anode was on the right and the cathode on the left mastoid (Saj et al., 2006). Due to our finding that the perceived verticals deviate to the side of the cathode for up to 15 minutes after stimulation, it should be taken into account that both online effects and aftereffects could influence the therapeutic effect. In some cases it might be useful to reconsider the placement of the electrodes and setting of parameters.

This pilot study has a few limitations. One is that we did not control the subjects' trunk and head positions during verticality adjustments. Even though GVS is known to affect head and trunk orientation, its influence on verticality adjustments is controversial (Funk, Finke, Muller, Utz, & Kerkhoff, 2010; Mars et al., 2005; Tarnutzer, Bockisch, & Straumann, 2010; Wardman, Taylor, et al., 2003). Another limitation is that the order of the different verticality assessments in experiment 1 was not randomized. The SVV and SHV adjustments were performed in a fixed sequential order on day 2. This might have biased the results, e.g. by adding up the stimulation effects, thus affecting the measures on day 2 more than those on day 1 (SPV). However, a recent study provides evidence against this, as repetitive GVS of up to 10 sessions was not more effective than a single session of GVS for improving neglect (Wilkinson et al., 2014).

2.2.5 Conclusions

Our results provide the first direct evidence that GVS has both online effects *and* aftereffects on the subjective verticals. While online effects persisted during the entire 20-minute stimulation interval, aftereffects lasted up to 15 minutes post stimulation with 1.5 mA direct stimulation. Persistent, reversed tilts of the subjective verticals after the termination of GVS might have crucial implications for the rehabilitation of spatial orientation deficits. Further studies are needed to investigate such aftereffects over a longer timescale and after repetitive stimulation.

2.3 Effects of galvanic vestibular stimulation on spatial neglect – A randomized controlled trial

2.3.1 Introduction

Neglect patients typically exhibit a rightward exploration bias as well as a disturbed perception of verticality. A new treatment for spatial neglect was first proposed at the end of the 1990s: GVS. It took however about another decade for further research to follow. Thus, although current evidence of GVS effects on neglect is promising, it is also relatively scarce. Ameliorations of neglect during GVS were found for both a CL- and CR-set-up, though in different ways depending on the type of neglect-related deficit.

For a line-crossing task, Rorsman et al. (1999) demonstrated better left-sided performance in neglect patients during CR-GVS. Supporting this, two recent studies also reported improvements on spatial exploration during and after CR-GVS (Wilkinson et al., 2014; Zubko et al., 2013). These findings are consistent with the aforementioned neuroimaging results: In right-handed subjects, CR-GVS activates the right hemisphere; thereby more attention can be directed towards the left hemispace again (Fink et al., 2003) (see Chapter 1.2.3.3 for more details). Nevertheless, therapeutic effects were also found for CL-GVS. In a sham-controlled trial with neglect patients and controls, both CL- and CR-GVS led to better performance on a line bisection task. Improvements were still greater during CR- than CL-GVS (Utz, Keller, Kardinal, et al., 2011). A case study also reported similar improvements on complex figure copying during CL- and CR-GVS. It should be noted though, that the patient exhibited a specific figure copying deficit; with a history of neglect, but no signs at testing anymore (Wilkinson, Zubko, Degutis, Milberg, & Potter, 2010).

While for the rightward exploration bias therapeutic effects during CR- outweigh those during CL-GVS, the opposite is the case for deviations of the subjective verticals. During GVS, neglect patients' visuo-tactile verticality adjustments (in the frontal plane) shifted towards the anode. Since neglect patients' subjective vertical in the frontal plane is usually shifted contralesionally, their shifts were ameliorated with the anode on the right mastoid (CL-GVS set-up) (Saj et al., 2006). Compared to healthy controls, these GVS-induced shifts were greater for right brain-damaged patients with and without neglect. Until now, the study by Saj et al. (2006) is the only one testing GVS-induced verticality shifts in neglect patients. Studies on healthy controls however have also found shifts of

both the subjective visual (SVV) and haptic vertical (SHV) towards the anode during stimulation (Lenggenhager et al., 2008; Mars et al., 2001; Mars et al., 2005; Saj, Honore, Bernati, et al., 2005). These effects were more pronounced in the visual modality.

Due to the mixed and sparse findings, it is still not entirely clear which stimulation set-up (CR vs. CL) is best for which type of neglect-related deficit. Other open questions concern the amount of GVS sessions and the aftereffects of stimulation. Only recently, two studies reported first evidence on beneficial effects of repetitive CR-GVS on neglect that lasted up to 4 weeks after the intervention (Wilkinson et al., 2014; Zubko et al., 2013).

To investigate the therapeutic effectiveness of GVS we designed a randomized controlled trial (RCT) and aimed to clarify two questions: (a) Do 10-12 sessions of CL- or CR-GVS combined with standard therapy reduce neglect to a greater extent than 10-12 sessions of Sham GVS and standard therapy? (b) Do these improvements remain stable until 2 and 4 weeks post-treatment?

2.3.2 Methods

Study design

This study was a randomized, controlled, double-blind trial using minimization. Treatment (GVS) was administered as an add-on therapy to conventional treatment. The study protocol was approved by the ethics committee of the Ludwig-Maximilians-University. All participants provided their written informed consent.

Participants

24 stroke patients were recruited from the Schoen Clinic Bad Aibling. Patients were screened at admission to the clinic according to the following inclusion criteria: (a) first-ever right-hemispheric stroke; (b) signs of left-sided spatial neglect (Neglect test (NET, German version of the Behavioral Inattention Test) score ≤ 135 , cut-off for mild neglect or suspicion of neglect); (c) age > 18 years. Exclusion criteria were as follows: (a) any metal implants; (b) brain tumor; (c) previous epileptic seizure; (d) craniotomy; (e) degenerative or psychiatric disorder; (f) unable to perform the NET. Since visual field defects often co-occur with neglect (in 70-90% (Kerkhoff, 1999; Vallar & Perani, 1986))

and are often not clearly distinguishable at an early stage of the rehabilitation process, patients with visual field defects were not excluded.

Fig. 10 summarizes the patient recruitment and retention. All patients were hemiparetic, and thus right-handed. Demographic and clinical data and statistical comparisons are shown in Table 4 (Chapter 2.3.3).

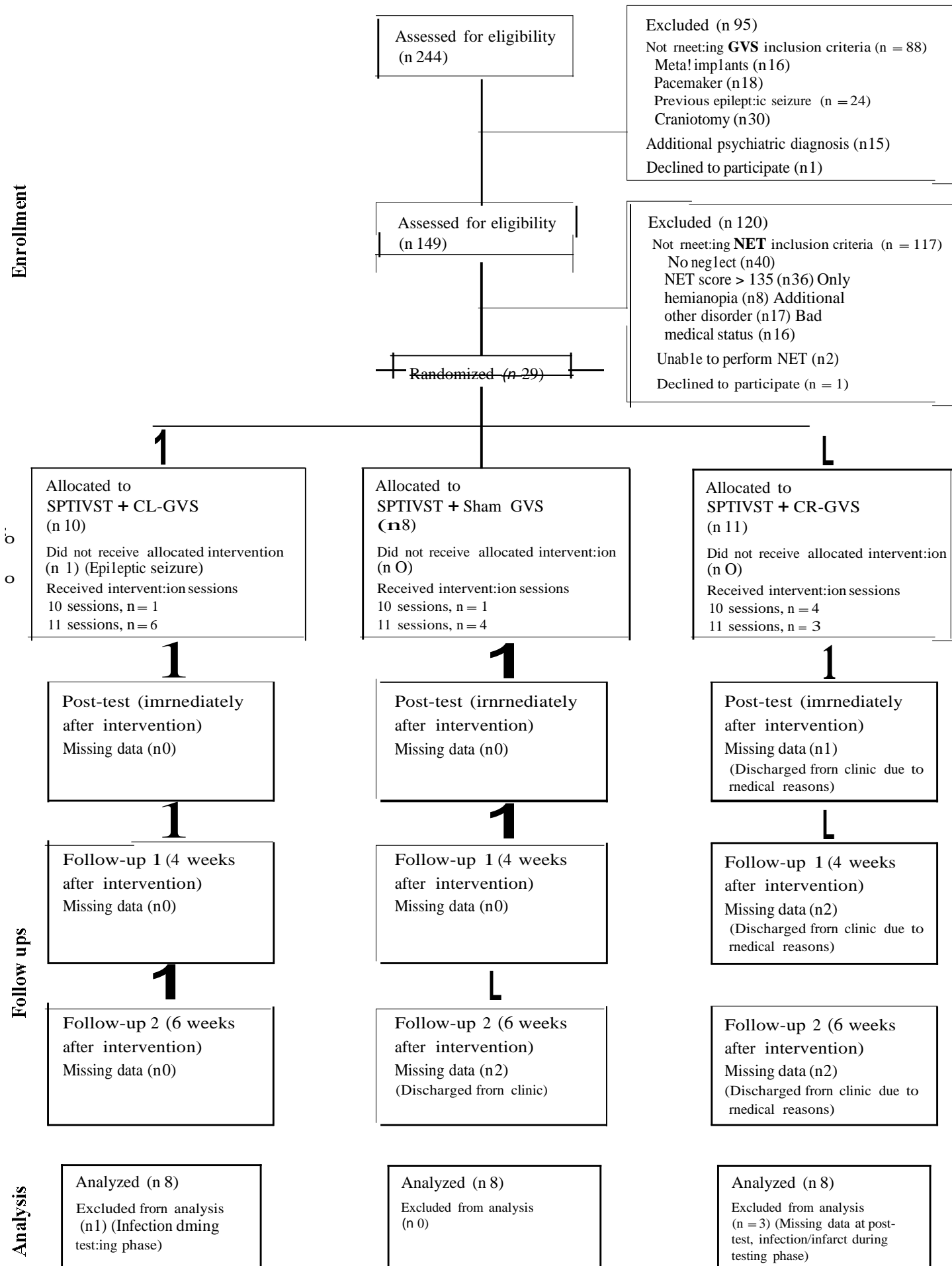


Figure 10. Flowchart of patient screening, enrollment, allocation, follow-ups and analysis

GVS, galvanic vestibular stimulation; NET, neglect test; SPT, smooth pursuit eye movement therapy; VST, visual search training; CL, GVS with the cathode on the left mastoid; Sham, only 30s of GVS; CR, GVS with the cathode on the right mastoid.

Randomization and Masking

After participants completed the baseline assessment and were qualified for inclusion, they were randomly allocated to the treatment groups by the research coordinator who drew cards from a sealed envelope. Since patients with more severe spatial neglect might respond differently to the interventions than those with milder impairments, we employed randomization with minimization (Scott, McPherson, Ramsay, & Campbell, 2002). Minimization was based on NET scores. The NET score range for inclusion was subdivided into three strata: 0-45, 46-90, 91-135. Minimization was performed by a post-doctoral researcher otherwise not involved in the study. We allocated 7 patients using minimization.

Participant screening and the intervention were administered by the study coordinator. Outcome measures were assessed by trained neuropsychologists, masked to treatment allocation and not otherwise involved in patients' treatment. Patients were also blinded to the allocated intervention. Figure 9 summarizes patient recruitment, allocation and retention.

Outcome Measures

All outcome measures were assessed at baseline, immediately after treatment (Post-test), two (Follow-up 1, FU1) and four (Follow-up 2, FU2) weeks after the end of the treatment.

Primary outcome measures

To assess signs of spatial neglect, we used the 'Neglect test' battery (NET), a German adaptation of the Behavioural Inattention Test (BIT). The NET consists of 17 subtests (e.g. cancellation, reading, copying and picture scanning tasks). Scores are given for every correct answer/item on each subtest (raw score), thus higher scores indicate better performance. The raw scores of each subtest are then standardized and summed up to a total, standardized NET score. This total score ranges from 0 to 170 points, with three sectors: 0-72 = very severe spatial neglect, 73-135 = severe neglect, 136-166 = mild neglect/ neglect suspicion.

To investigate abilities closely related to everyday life, we used a visuo-tactile search task. A rectangular board (120 x 60 cm) with 18 objects (e.g. pen, button etc.), which were evenly distributed in space (each third of the board comprised 6 objects), was placed in front of the patient. Patients were asked to find 9 objects (3 targets in each third) as quickly as possible within a time limit of 30s for each target. Number of detected objects and search times were assessed and summed up for each third (left, middle, and right). Two versions with different targets were alternated between the four assessments. The search time for left-sided objects was used as the outcome variable. Lower search times indicate better performance.

Secondary outcome measures

The subjective visual (SVV) and haptic vertical (SHV) were used to assess spatial orientation. The SVV was assessed with the so called bucket test, in which subjects indicate when they perceive a dark line as vertical (see (Zwergal et al., 2009a) for further details). The SHV was measured with a rod (27 cm long, 1 cm wide) which was mounted onto a vertical plate. Subjects' task was to adjust the wooden rod to their perceived vertical position. Subjects were seated and blindfolded and always used their right hand. Preventing any reference cues, they were not allowed to touch the device's plate or the desk. A scale was mounted onto the plate to record subjective vertical adjustments. For both measures, the mean deviation, the unsigned, averaged error (absolute error regardless of direction), and the range (difference between maximum and minimum values) were calculated. For the mean deviation, negative values indicate leftwards, positive values rightwards deviations.

Intervention

The treatment started on the same day or the day after baseline assessments and consisted of daily training sessions (20 minutes), 5 days a week for a total of 10 to 12 sessions.

As standard therapy all patients received smooth pursuit eye movement training (SPT) and visual scanning training (VST). Both training programs were presented on a 14.1 inch laptop monitor (refresh rate of 60 Hz). For SPT, computer-generated random displays of 350 dots (blue on a white background) that were moving coherently towards the left hemispace (speed: 6.9°/s), were presented. Patients were instructed to look at the displays and make smooth pursuit eye movements towards the direction of motion and return to the rightward side of the screen whenever they had reached the leftward border of the screen. For VST, different exercises from the therapy-program Cogpack® were used to train exploration to the left hemispace. VST programs and their difficulty level were adjusted individually depending on patients' capabilities.

Simultaneously, patients received GVS or sham stimulation. Bilateral bipolar GVS was delivered by a battery-driven, direct current stimulator (neuroConn Ilmenau, Germany). Two electrodes (anode and cathode) were covered with sodium-chloride soaked sponges (30 cm² each) and placed over both mastoids. Polarity placements were changed for each of the three stimulation conditions. For CL-GVS, the cathode was placed on the left and the anode on the right mastoid. This electrode placement was reversed for CR-GVS. In the Sham-GVS condition, the electrodes were positioned as in the CL-GVS condition; however only 30s current (at 1.5 mA) was applied. For CL- and CR-GVS, current was ramped up (in steps of 0.1 mA/sec) to 1.5 mA, kept there for 20 minutes, and ramped down again (in steps of 0.1 mA/sec). Conforming with established safety limits, subjects were only stimulated for 20 minutes with 1.5 mA.

Apart from the intervention, patients received occupational and physiotherapy, but no other specific neglect training.

Data analyses

To handle missing data of the NET and search task (4 missing data points), we originally fit a regression line to the available data points of each affected patient. Since the regression line did not represent the data well, we applied the last observation carried

forward (LOCF) technique. For the SVV and SHV, there were more missing data points since some patients were not able to perform the tasks at baseline (in total SVV: 9; SHV: 5). Baseline measurements were therefore substituted with the group mean. Except for one case, all patients were able to perform the tasks after the intervention. Accordingly, LOCF was applied for missing data of those time points.

Data analyses were computed with SPSS (version 17.0, SPSS Inc). To investigate differences in treatment effects over time, repeated-measures ANOVAs with the between-subject factor treatment (CL-GVS, Sham-GVS, CR-GVS) and the within-subject factor time point (Baseline, Posttest, Follow-up 1, Follow-up 2) were conducted for all outcome measures. In case of significant results, subsequent post-hoc tests were performed (Bonferroni corrected). P-values of less than 0.05 were considered significant.

2.3.3 Results

Group comparisons of demographics and baseline performance

The three groups did not differ significantly regarding age ($F(2,21) = 0.2, p > 0.05$), sex ($\chi^2(2) = 1.37, p > 0.05$), visual field defects ($\chi^2(6) = 10.0, p = 0.13$), baseline scores of the NET ($F(2,21) = 0.05, p > 0.05$) and the search task ($F(2,21) = 1.21, p > 0.05$), and number of treatment sessions ($F(2,21) = 0.55, p > 0.05$). Groups however differed in time since lesion ($F(2,21) = 3.69, p < 0.05$). Post hoc tests showed differences between the CL-GVS ($M = 1.9$ months, $SD = 0.9$) and Sham-GVS ($M = 1.0$ months, $SD = 0.26$) group ($t(14) = 2.7, p = 0.017$). Clinical and demographic data are shown in Table 4.

Table 4

Clinical and demographic data and primary outcome measures at baseline

Sample size (p)	Cathode left group (n = 8)	Sham group (n = 8)	Cathode right (n= 8)	Statistical comparison
Stroke etiology (ischemic/ hemorrhagic)	3/5	8/0	7/1	-
Months since stroke (mean; range)	1.9 (1.1-3.9)	1.0 (0.7-1.5)	1.3 (0.4-2.2)	0.042
Age (years; range)	70.6 (55-80)	70.4 (45-82)	73 (61-83)	0.82
Sex (male/female)	2/6	4/4	4/4	0.50*
Visual field defects (no defects, hemianopia, quadrantanopia, no examination)	3/3/2/0	1/5/0/2	2/6/0/0	0.13*
NET baseline score (range)	93 (29-124)	89 (22-123)	94 (47-134)	0.95
Visuo-tactile search task (left side; sec)	38.9	49.1	59.7	0.32
No. of treatment sessions (10/11/12)	11 (1/ 5/ 2)	11 (1/ 4/ 3)	11 (3/ 3/ 2)	0.59

p: statistical significance (one-way ANOVAs; *chi-square test for categorical data)

Primary outcome measures

NET

There was a significant main effect of time point ($F(3, 63) = 44.96, p < 0.01$). Subsequent analyses showed baseline scores ($M = 91.6$ points) to be different from all other time points (M for Post = 120.8, FU1 = 125.8, FU2 = 126.6 points) ($F(3,19) = 29.36, p < 0.01$) (Fig. 11).

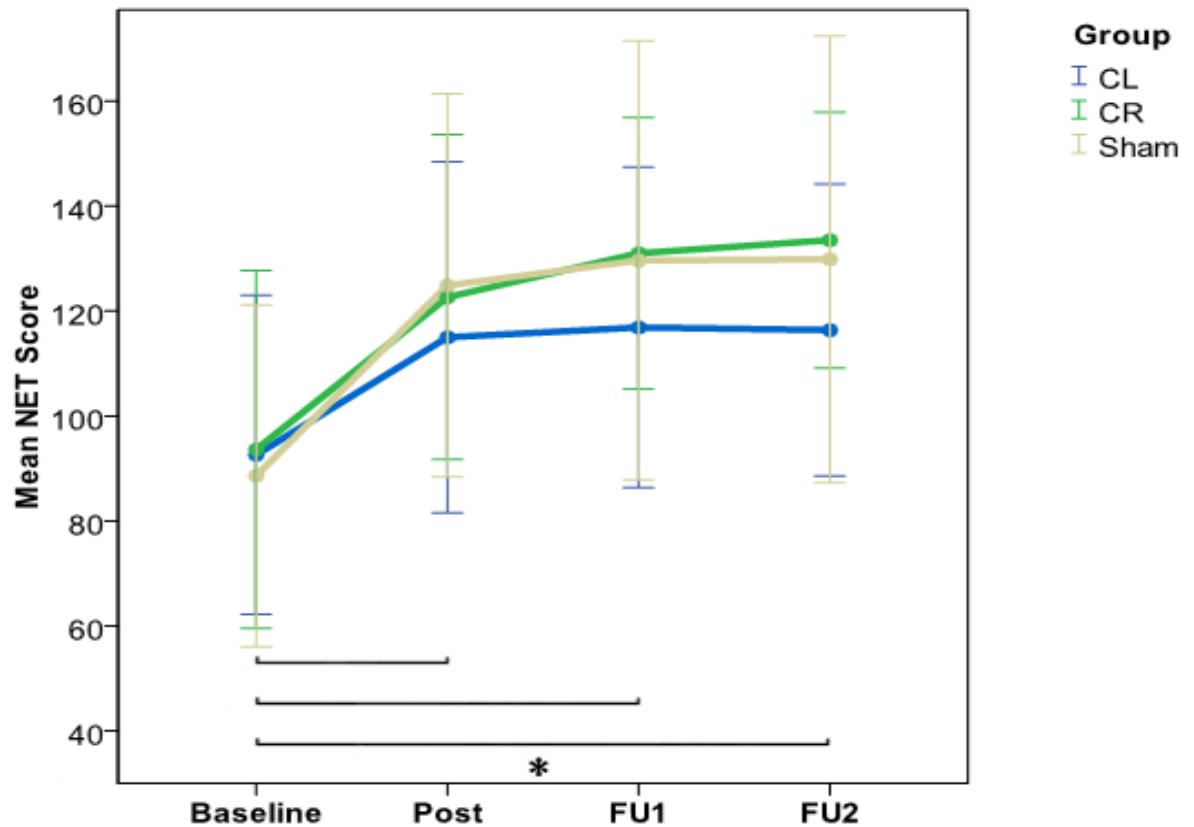


Figure 11 NET scores

NET scores (mean \pm standard error) are shown as a function of time point and group. Higher scores indicate better performance. * $p < 0.05$ (main effect of time point)

Visuo-tactile search task

There were a significant main effect of time point ($F(3, 63) = 19.98, p < 0.01$) and interaction of time point and group ($F(6, 63) = 2.34, p < 0.05$). Post-hoc comparisons revealed that search times at baseline (48.7s) differed from all other time points (30.7s, 24.7s, 23.1s) ($F(3,19) = 19.00, p < 0.01$). To break down the interaction, Helmert contrasts were performed comparing each time point to all ensuing ones. These revealed a significant interaction for the group when comparing search times at baseline level to the other time points ($F(2,21) = 3.47, p = 0.05$). These effects reflect that search times decreased more from baseline to the following time points for the CR-GVS group compared to the CL-GVS group, and slightly better than the Sham-GVS group (Fig. 12).

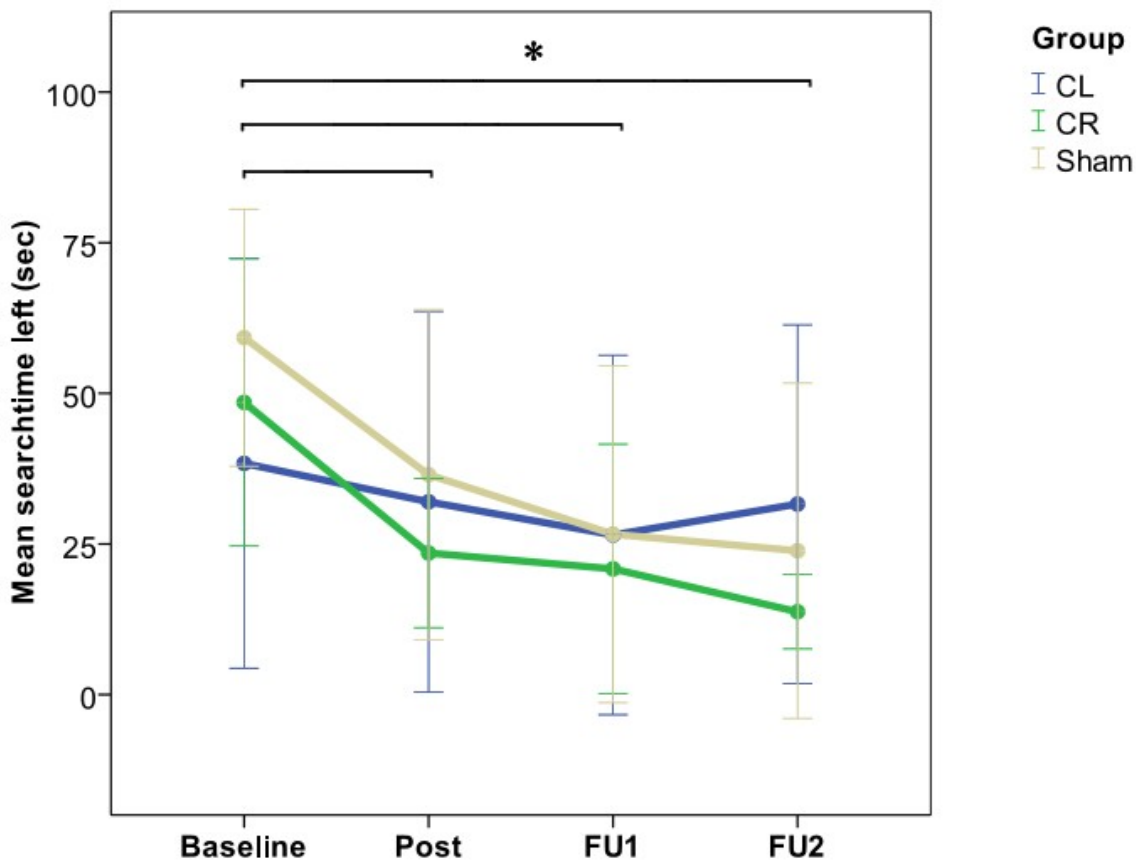


Figure 12 Search times for left-sided objects

Search times (mean \pm standard error) are shown as a function of time point and group. Shorter times indicate better performance. * $p < 0.05$ (main effect of time point and an interaction of time point and group)

Secondary outcome measures

SVV

There were no significant differences for the mean SVV deviations (Fig.13). For the constant errors, sphericity was violated and Greenhouse-Geisser correction was applied. There was a significant main effect of time point ($F(2.18,45.86) = 5.43, p < 0.01$). Post-hoc comparisons revealed that error sizes at baseline (9.04°) differed from FU1 (5.42°) and FU2 (5.80°) error sizes ($F(3,19) = 13.82, p < 0.01$) (Fig. 14). For the ranges, there were a significant main effect of time points ($F(3,63) = 5.38, p < 0.01$) and an interaction of time points and group ($F(6,63) = 2.48, p < 0.05$). Regarding the time points, ranges at baseline (26.11°) differed from all other time points (M for Post: 17.38° , FU1: 16.96° , FU2: 16.46°) ($F(3,19) = 7.46, p < 0.01$). The interaction indicates that the treatments had different effects on SVV ranges depending on the time point. To break down this interaction, Helmert contrasts were performed comparing each time point to all ensuing ones. These revealed a significant interaction for the group when comparing SVV ranges at baseline levels to the other time points ($F(2,21) = 7.26, p < 0.01$). These effects reflect that SVV ranges in the CR-GVS group reduced more from baseline compared to the other time points than the Sham-GVS and CL-GVS group. SVV ranges in the CL-GVS group stayed at an almost constant level over all time points (Fig. 14).

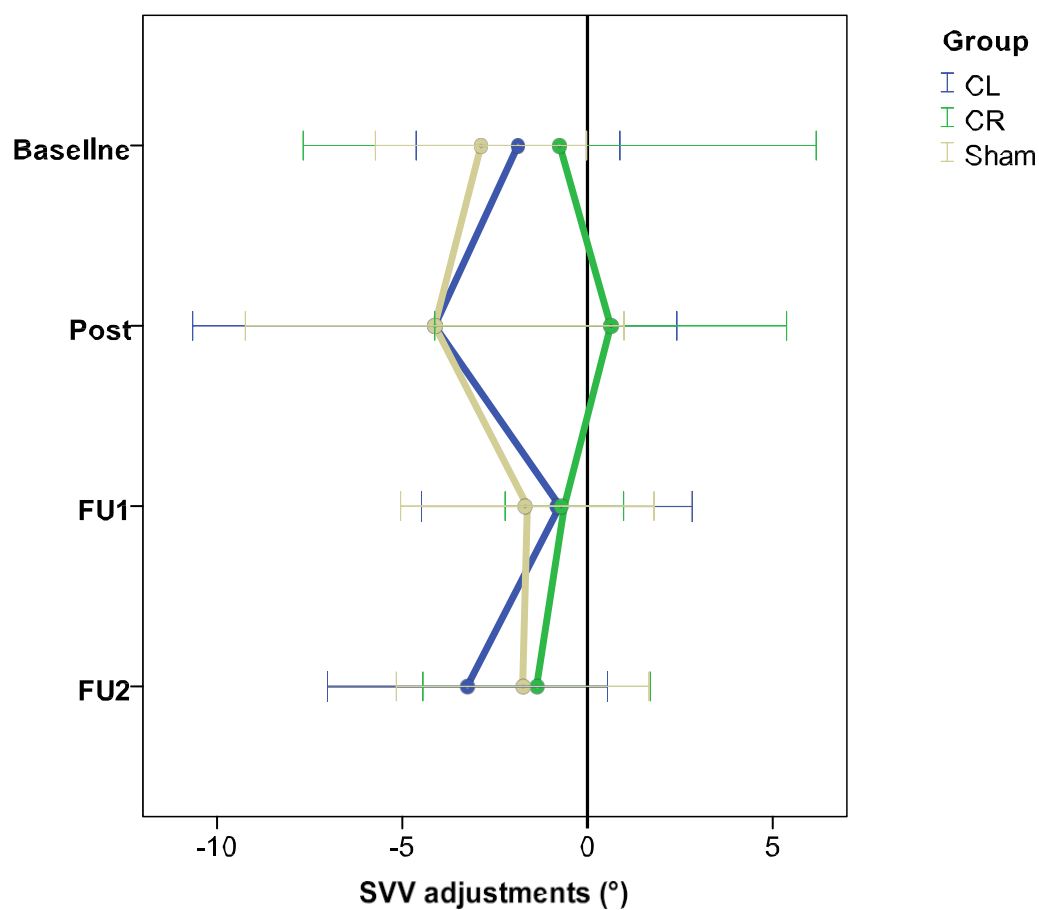


Figure 13 SVV adjustments

SVV adjustments (mean \pm standard error) are shown as a function of time point and group. Positive values indicate a tilt to the right or ipsilesional side, negative values a tilt to the left or contralesional side.

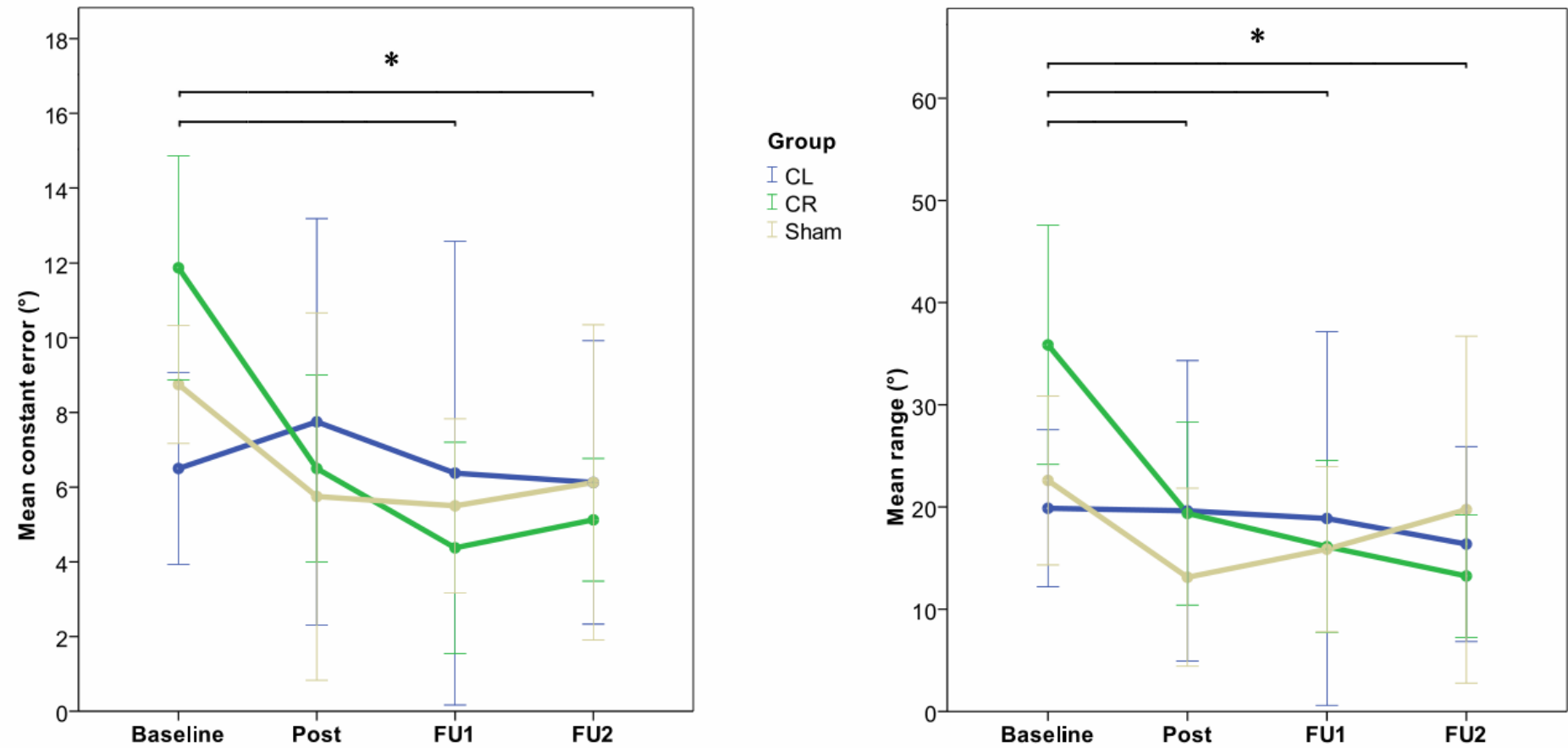


Figure 14 Constant errors and ranges of the SVV adjustments

SVV constant errors and ranges (mean \pm standard error) are shown as a function of time point and group. * $p < 0.05$ (constant error: main effect of time point; range: main effect of time points and an interaction of time point and group)

SHV

There were no significant differences for the mean SHV deviations (Fig. 15). For the constant error, sphericity was violated and Greenhouse-Geisser correction was applied. There was a significant interaction of time point and group for the constant error ($F(3.67, 38.71) = 2.71, p < 0.05$). To break down this interaction, Helmert contrasts were performed comparing each time point to all ensuing ones. These revealed a significant interaction for the group when comparing SHV constant errors at baseline levels to the other time points ($F(2, 21) = 3.72, p < 0.05$). These effects reflect that SHV constant errors reduced in the CR-GVS and Sham group, while they even increased in the CL-GVS group. For the CR-GVS group these reductions remained constant until FU2, while they slightly increased again for the Sham-GVS group (Fig. 16). There were no significant differences for the range (Fig. 16).

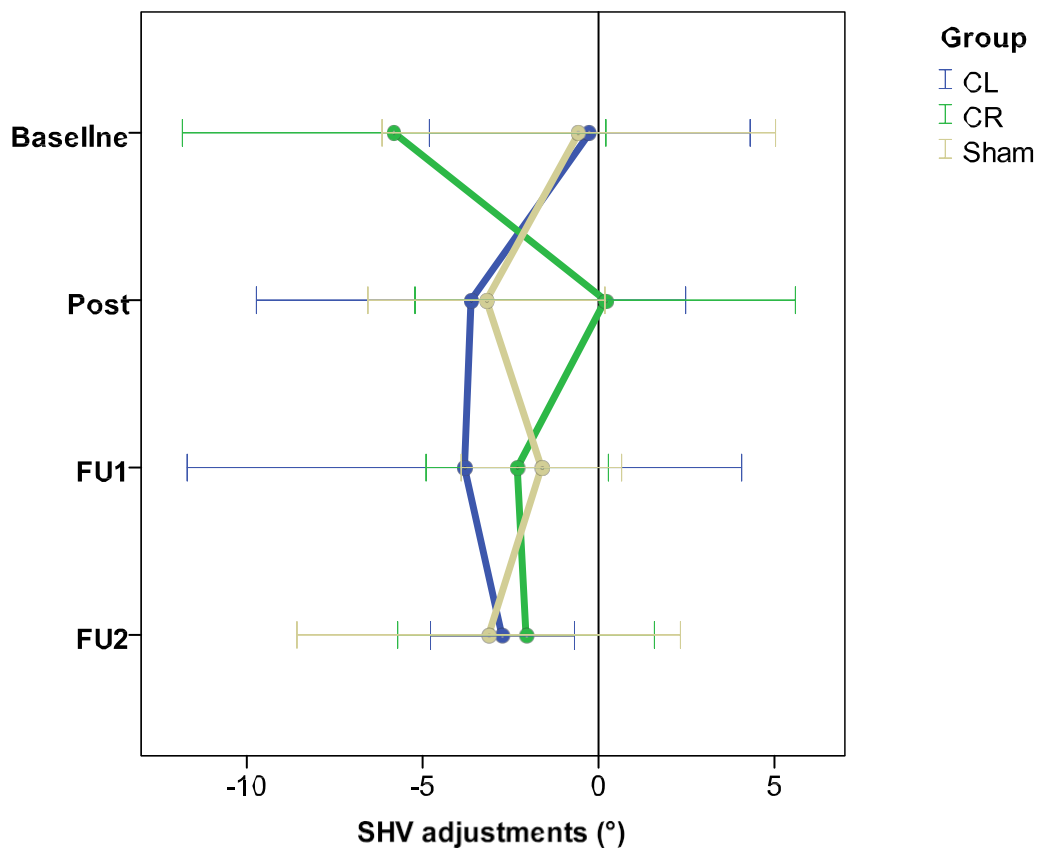


Figure 15 SHV adjustments

SHV adjustments (mean \pm standard error) are shown as a function of time point and group. Positive values indicate a tilt to the right or ipsilesional side, negative values a tilt to the left or contralesional side.

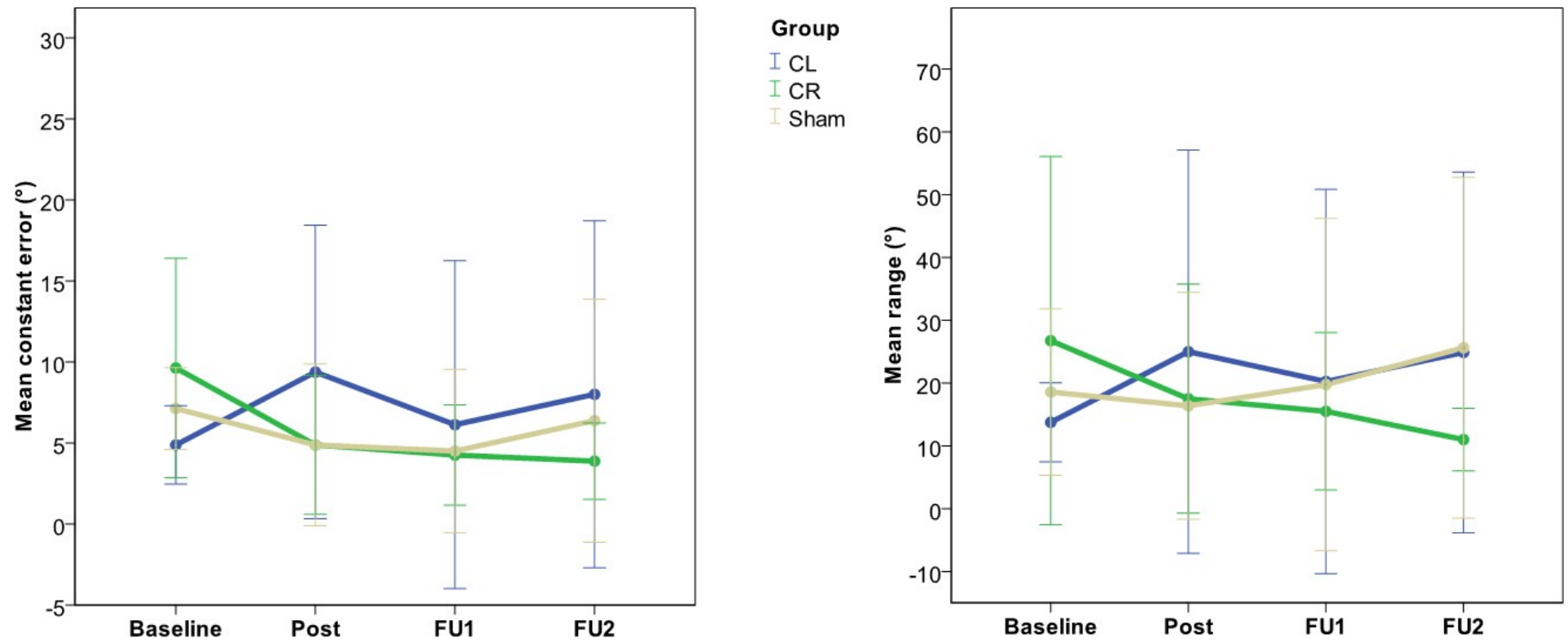


Figure 16 Constant errors and ranges of the SHV adjustments

SHV constant errors and ranges (mean \pm standard error) are shown as a function of time point and group. (constant error: interaction of time point and group; range: no significant effects)

2.3.4 Discussion

This is the first RCT investigating the effectiveness of GVS combined with standard therapy. Our results indicate that after the intervention period the simultaneous administration of GVS had not improved neglect significantly more than standard therapy alone.

Primary outcome measures

Immediately after the intervention period, all groups exhibited improved NET scores and search task times. There was however no additional beneficial effect of GVS. Despite that, rehabilitation in the two GVS groups appeared to progress differently. Compared to the baseline, intra-individual NET score improvements of the CR-GVS group were 1.7 times greater than those of the CL-GVS group. Additionally, the CR-GVS group kept improving over the entire study period, while the CL- GVS group stayed at an almost constant level after post-testing (see Fig.11). Consistent with that, we found greater improvements on the visuo-tactile search task for the CR-GVS and the Sham-GVS group compared to the CL-GVS group (Fig.12).

A superior effect of CR-GVS on neglect is consistent with previous neuroimaging results. In right-handed subjects CR-GVS led to unilateral, right-hemispheric vestibular cortices activation while CL-GVS activated vestibular cortices bilaterally (Fink et al., 2003). Accordingly, in right-handed neglect patients CR-GVS is hypothesized to alleviate their deficits by activating areas in the right, damaged hemisphere, which can direct attention also towards the left side again. Contrary to that, the bilateral activation of CL-GVS would rather preserve the activity imbalance between the hemispheres in neglect (Brandt, Glasauer, Strupp, & Dieterich, 2009). It has to be noted though that GVS-induced cortical activation depends on subjects' handedness (Dieterich et al., 2003) and has so far only been investigated for right-handed healthy controls (Fink et al., 2003). Thus, CR-GVS might not lead to therapeutic effects in left-handed neglect patients.

Despite these promising findings for healthy controls, neglect behavior was not ameliorated significantly more by GVS than standard therapy in our patient sample. In the following paragraphs, possible reasons for this will be discussed.

Firstly, the aforementioned cortical activation might not be induced to the same extent or even be distributed differently in brain-damaged patients. Previous neuroimaging

findings were obtained with healthy controls. To date, it is not known what GVS activates in a lesioned brain, and how it is related to the lesion locations.

Secondly, our study measured after- instead of online effects. Previously shown therapeutic effects on neglect were mainly obtained during stimulation (Rorsman et al., 1999; Utz, Keller, Kardinal, et al., 2011; Wilkinson et al., 2010). It is thus possible that there is no, only a small, or a shorter lasting (than ~24h) transfer effect of increased, left-sided exploration after stimulation is turned off. Contrary to these possibilities, a recent study found beneficial effects of repetitive CR-GVS up to 4 weeks after the intervention (Wilkinson et al., 2014). Interestingly, one session was not more effective in ameliorating neglect than 10 session of CR-GVS. This is contrary to the common approach of repeated administration for maximizing the rehabilitation outcome. Wilkinson et al. (2014) propose that one session of CR-GVS might be sufficient for inducing long-lasting synaptic changes. An early case study however found two blocks to be superior to one block of stimulation (Wilkinson et al., 2010).

Thirdly, our add-on design combines two different therapeutic approaches and might thereby lead to an underestimation of the effect of each of them. Other studies combining different therapies have demonstrated such effects: Even if a given therapy had proven effective, there was often no gain in effectiveness from combining it with another, equally effective therapy (Lisa, Jugheters, & Kerckhofs, 2013). Both visual search training and neck muscle vibration did not lead to greater improvements when administered simultaneously with prism adaptation (Guinet & Michel, 2013; Keller, Lefin-Rank, Losch, & Kerkhoff, 2009). Similarly, using two forms of limb activation training did not reduce neglect symptoms any more than using just one form (Fong et al., 2013; Pitteri, Arcara, Passarini, Meneghello, & Priftis, 2013). Despite of having a combined effect of different therapies, we used an add-on design to be able to administer at least one evidence-based therapy (SPT & VST) to each patient over the two-week intervention period. Based on GVS-induced online effects, estimated effect sizes were large enough to still become apparent.

Finally, patients' head position might have contributed to our non-significant effects of GVS. According to Fitzpatrick & Day (2004), the subjects' head position determines in which position the vestibular organs are stimulated and thus also the associated perception. As described above, the GVS-induced perceptions are predicted with a vector model. With the head upright and a CR-GVS set-up, subjects would perceive a large head movement in the frontal plane and a smaller movement in the horizontal plane

– both towards the right side. A larger movement in the horizontal plane would however be elicited with the head pitched forwards or backwards. Since neglect's exploration deficits are typically assessed in the horizontal plane, it could be beneficial to manipulate their perception via GVS in that plane. Until now, however, it is not entirely clear what the behavioral response to a rotation perception in the horizontal plane is in patients. Based on previous findings, GVS-induced behavioral responses are directed in the opposite direction to the perceived rotation, that is towards the anode (St George & Fitzpatrick, 2011). CR-GVS could thus induce an orientation of the head, and possibly also of attention, towards the anodal, left side.

However, it is not known whether transduction, cortical activation, and perception of the GVS signal works similarly in healthy controls and neglect patients.

Secondary outcome measures

At baseline, patients' SVV and SHV were on average slightly (max. of 7°) shifted to the contralesional side. Previously, deviations ranging from 5 to 10 degrees have been reported for neglect patients (Funk, Finke, Muller, Preger, et al., 2010; Funk, Finke, Muller, Utz, et al., 2010; Funk et al., 2011; Kerkhoff, 1999; Kerkhoff & Zoelch, 1998; Saj, Honore, Bernati, et al., 2005). One possible explanation for our small deviations could be that some patients did not only exhibit neglect, but also pusher behavior. In pusher behavior, patients actively push themselves away from the non-paralyzed side (D. A. Perennou et al., 2008). The syndrome often co-occurs with neglect (D. Perennou, 2006) and these patients' subjective straight ahead and SVV was found to deviate to ipsilesional, not contralesional space like in neglect (Honore, Saj, Bernati, & Rousseaux, 2009; Saj, Honore, Coello, & Rousseaux, 2005). Since we did not assess pusher behavior, deviations in our data might have been averaged out by some ipsilesional deviations of simultaneous neglect and pusher behavior.

Overall, there were no significant changes in the mean deviation of both the SVV and SHV for any of the three groups. When inspecting the data, however, both verticals had shifted some degrees towards the side of the cathode at post-test compared to baseline. This shifted towards baseline values again over the 2-and 4-week follow-up, but did not entirely reach them. Since Sham-GVS included 30 seconds of CL stimulation, slight leftwards shifts were observed. Despite the lack of statistical significance, these shifts are consistent with aftereffects that we found in another experiment (see section 2.2. for

a detailed description). The subjective visual, haptic and postural vertical of neglect patients and age-matched healthy controls shifted towards the cathode 3 minutes after GVS. In the haptic modality, these aftereffects lasted up to at least 15 minutes (unpublished results). Such reverse aftereffects towards the cathode are well known from GVS-induced oculomotor responses and body movements (H.G. MacDougall et al., 2002; H. G. MacDougall et al., 2003; Severac Cauquil et al., 2003). These findings are consistent with our observations in the present study. The present observations extend the presence of aftereffects in the subjective verticals from 3 minutes to at least 24 hours post stimulation.

Interestingly, we found significant changes in error and range sizes of the SVV and SHV. This supports the notion that GVS is affecting verticality perception. While SVV error and range sizes decreased over time, ranges did so differently for the groups. The Sham- and CR-group's ranges decreased, with greater improvements for the CR-group. Ranges of the CL-group only changed minimally (Fig.14). Similar, but less pronounced effects, were obtained for the SHV (Fig.16). For the SHV, constant errors were found to decrease at differently over time. While constant errors reduced in the CR-GVS and Sham group, they even increased in the CL-GVS group. For the CR-GVS group these reductions remained constant until FU2.

Reductions of error and ranges in the CR-GVS group are consistent with the aforementioned rightward shifts after the application of GVS. The slight deviation in verticality judgments to the left is thus reduced by shifts towards the right. Contrary to that, patients' deviations are exacerbated by CL-GVS as it shifts verticality judgments even more towards the left. Error and range sizes of the Sham-GVS group do not seem to be affected by the short CL stimulation interval since they generally decrease over time.

Our findings suggest that aftereffects are crucial to be considered in the rehabilitation of neglect patients' verticality deficits. So far, therapy was based on effects during GVS. The contralesional deviation in the subjective verticals was ameliorated during CL-GVS since the verticals shift toward the anode (on the right) during stimulation (Saj et al., 2006). The present results however suggest that rehabilitation for deviations in the subjective verticals should be approached based on the aftereffects of GVS. Since verticality deficits are associated with neglect (Kerkhoff, 1999; Yelnik et al., 2002),

rehabilitation of the subjective verticals could possibly enhance the rehabilitation of other deficits of neglect.

A few limitations of this RCT should be mentioned. The head position was not controlled for since the main purpose of this clinical trial was to investigate therapeutic effects of GVS. Thus we sought to also include neglect patients who are still too impaired to use a head rest. Another limitation is the difference in time since lesion between the CL-GVS and Sham-GVS group. The earlier inclusions time of patients in the Sham-GVS group could possibly explain that they profited from the treatment as much as the other two treatment groups. Overall, the limited number of subjects could hamper the generalizability of our findings.

2.3.5 Conclusions

Results of this RCT indicate that the simultaneous administration of GVS with standard therapy is not more effective than standard therapy alone for the treatment of spatial deficits. Verticality perception was influenced by GVS: The magnitude of both the error and the variability of patients' verticality adjustments decreased, in the visual vertical up to four weeks post treatment. Future research is needed to investigate a transfer of these improvements to other, related types of deficits, such as spatial orientation and posture.

3. Discussion

Within the framework of this doctoral thesis, I investigated neglect patients' different types of deficits and how these are affected during and after the application of GVS.

This work offered new information on temporal processing deficits in right brain-damaged patients and their association with spatial deficits. Furthermore, this thesis contributed to the scientific knowledge on the online effects and aftereffects of GVS. A randomized controlled, double blind trial offered new insights into the effectiveness of GVS for different types of neglect-related deficits.

In the following chapters the results will be discussed in detail and compared to the existing literature. Particular attention is paid to temporal deficits and their association with space and the use of GVS as a therapeutic tool.

3.1 Association between time and space

Neglect patients' problems with time have been remarked upon during the everyday clinical routine for a long time, although rigorous experimental investigation of these deficits in the absence of confounding stimuli has been lacking. Thus, study 1 investigated different groups of right brain-damaged patients' performance on a time estimation and bisection task of multi-second intervals (6-24s). While all right brain-damaged patients were impaired on temporal processing, the deficits of patients without spatial deficits were distinct from those of patients with current or previous spatial deficits. Indicating an association between time and space, all patients with spatial deficits were also impaired on temporal processing. However, the compensation of previous spatial deficits did not entail improvements of temporal deficits.

Experimental research on the relationship between time and space has greatly intensified since Walsh (2003) proposed 'A Theory of Magnitude' (ATOM). According to the ATOM, different types of magnitudes are computed with a common metric by a generalized magnitude system. Magnitudes included in this magnitude system are those that can be described as "'more than' or 'less than'" (Walsh, 2003, p. 484): space, time and quantity. The suggested location of this magnitude system in the brain is the inferior

parietal cortex. Apart from the shared metric and neural substrate, each magnitude is also assumed to have some idiosyncratic, independent aspects.

Consistent with this idea, we also found indications for independent mechanisms of time and space. Right brain-damaged patients who never had any spatial problems, did have difficulties on both time estimation and bisection. Similarly, patients who exhibited temporal deficits of the same nature, did either currently have spatial deficits or had compensated previous spatial deficits. Thus, the presence of spatial deficits alone cannot predict the presence of temporal deficits. The finding that all patients with spatial neglect also exhibited temporal deficits, however, indicates an interaction between time and space. Interestingly, spatial deficits could be compensated without having an effect on the temporal deficits. This suggests that the association between spatial tasks and our time estimation and bisection task is not very strong. Since our experiment was not primarily designed for identifying processing pathways, these interpretations would need further confirmation from additional studies.

Previous studies on healthy controls and neurological patients have demonstrated both independent and shared processing routes for time and space (Cappelletti et al., 2009, 2011; Vicario et al., 2008). The interaction between the different magnitudes seems to be asymmetrical. While temporal judgments were strongly influenced by spatial information, this was not the case vice versa (R. Bottini & Casasanto, 2010b; Casasanto & Boroditsky, 2008; Casasanto et al., 2010; Xuan et al., 2007). Other evidence demonstrated that temporal processing can be influenced by techniques that are known to manipulate spatial processing. While optokinetic stimulation (Vicario, Caltagirone, & Oliveri, 2007), prism adaptation (Frassinetti et al., 2009), and rTMS (Oliveri et al., 2009) modulated temporal processing in healthy controls, prism adaptation could also ameliorate temporal deficits in right brain-damaged patients (Magnani et al., 2011; Oliveri et al., 2013).

Based on these findings, time was hypothesized to be represented in the brain in a spatial manner, that is on a mental time line. Just like on the mental number line, shorter time intervals are represented on the left, and longer time intervals on the right side. Supporting this, the bisection of temporal and spatial intervals was found to be processed in the same cortical area – the right posterior parietal cortex (Koch et al., 2009; Oliveri et al., 2009). Inhibiting the right posterior parietal cortex with repetitive transcranial magnetic stimulation (rTMS) during a time bisection task in healthy controls led to

deviations similar to those observed in neglect patients. Remarkably, subjects only exhibited deviations when rTMS was applied during the retrieval of half of the previously encoded time interval (Oliveri et al., 2009).

As part of his first proposal of the ATOM, Walsh (2003) suggested the inferior parietal cortex as the neural substrate of magnitude processing. Succeeding studies investigated the cortical location more specifically and found the right inferior parietal sulcus (IPS) to be crucial (Coull & Nobre, 1998; Vogel, Grabner, Schneider, Siegler, & Ansari, 2013). Supporting this, the IPS is involved in the processing of all three magnitudes (time, space, and numbers) (Dormal, Andres, & Pesenti, 2012; Dormal, Dormal, Joassin, & Pesenti, 2012; Koch et al., 2009; Oliveri et al., 2009). Interestingly, a recent study demonstrated that transcranial random noise stimulation over parietal areas combined with a cognitive training improved numerosity, time and space discrimination. Even though the cognitive training only included numerosity discrimination tasks, improvements transferred to both time and space discrimination.

This was however only the case when the cognitive training was combined with parietal cortex stimulation, indicating the important role of this area in magnitude processing (Cappelletti et al., 2013).

3.2 Galvanic vestibular stimulation as a therapeutic tool

The use of GVS as a therapeutic tool was investigated in Study 2 and 3. Accordingly, the effects of GVS on verticality and spatial perception were examined in both healthy controls and right brain-damaged patients with neglect. Here, the findings presented in this thesis will be discussed in terms of the type of effect (online effect vs. aftereffect), the type of task (subjective verticals and spatial tasks), and stimulation and plasticity in the lesioned brain.

3.2.1 Online effects vs. aftereffects

During its application, GVS is known to induce perceptions of head movements. While the nature of the perception depends on the subjects' head position, the perceived movement is usually directed towards the cathode (see Chapter 1.2.3.2 for further details). Such head movements were demonstrated to cause a response counteracting

the perceived head movement that is directed in the opposite direction (towards the anode). Subjects' eyes (H.G. MacDougall et al., 2002; H. G. MacDougall et al., 2003; H. G. MacDougall et al., 2002; Schneider et al., 2000; Severac Cauquil et al., 2003; Watson et al., 1998; Zink et al., 1998), head (Mars et al., 2005) and body moved towards the anode during stimulation (Britton et al., 1993; Day, Severac Cauquil, Bartolomei, Pastor, & Lyon, 1997; Fitzpatrick & Day, 2004; Nashner & Wolfson, 1974; Tax et al., 2013; Wardman, Taylor, et al., 2003). One possible explanation for the therapeutic effects during GVS reported previously (Rorsman et al., 1999; Utz, Keller, Kardinal, et al., 2011; Zubko et al., 2013), might thus be such GVS-induced eye and head movements. Stimulation with a CR-GVS set-up causes movements of both the eyes and the head towards the left, anodal side. Such eye and head movements to the left side could thus be closely related to the ameliorations of neglect. Indeed, previous evidence has shown that head movements towards the left reduce symptoms of neglect (Schindler & Kerkhoff, 1997). Supporting the crucial role of eye movements, the subjective verticals typically shift towards the same direction (the anode) during stimulation as the eyes do (Study 2, Mars et al., 2001; Mars et al., 2005; Saj et al., 2006).

However, when stimulation is turned off, both movement perceptions (St George et al., 2011) and eye movements were found to reverse direction (H.G. MacDougall et al., 2002; H. G. MacDougall et al., 2003). While the perceived movement is directed towards the anode, the eye movements are directed towards the cathode after stimulation. Both movement perceptions (St George et al., 2011) and eye movements (H.G. MacDougall et al., 2002) had the same magnitude after switching stimulation off compared to switching it on. In line with these findings, we also found such reverse aftereffects for the subjective visual, haptic and postural modality: shifts towards the cathode after switching stimulation off (Study 2).

The underlying mechanism of such reverse aftereffects of GVS seems to be adaptation. Via adaptation (and via habituation) the perception of a continuous stimulus decreases over time (St George et al., 2011). A clear indication for adaptation is an aftereffect that is opposite to the online effect and occurs when a given stimulus is removed after a prolonged time period. By investigating the perception profiles during and after GVS, St George et al. (2011) found evidence for long-term adaptation of the vestibular signal. The adaptation seems to involve changes within the brainstem as well as the afferent system.

Regarding a therapeutic application of GVS, not only the presence, but also the time course of such reverse aftereffects is of great importance. In Study 2, we found that aftereffects of a 20-minute stimulation interval lasted up to at least 15 minutes for the subjective haptic vertical. Thus, the persistence of the aftereffects seems to be related to the duration of the preceding stimulation interval. Findings on GVS-induced eye movements and movement perceptions support this. A 6-min time constant was reported for the decay of reverse eye movement responses after a 5-minute stimulation interval (H. G. MacDougall et al., 2003). Similarly, rotation perceptions during and after stimulation had the same time course of decay (St George et al., 2011). In contrast to that, we found aftereffects up to at least 24 hours after 10-12 sessions of GVS (a total of 3.3-4 hours of stimulation) in Study 3. Despite the lack of statistical significance, the observable shifts towards the left and right are explicable by reverse aftereffects of GVS, similar to those reported in Study 2. While in the CL-GVS group, the subjective verticals were shifted towards the left at the Post-test, they were shifted towards the right in the CR-GVS group.

Until now, there are no studies on the underlying physiological effects of the online and aftereffects of GVS. Possible implications can only be drawn from investigations on tDCS, which is assumed to work via similar, physiological mechanisms. Evidence from tDCS suggests different mechanisms for effects during and after stimulation (for a review see Stagg & Nitsche, 2011). Effects during stimulation were modulated by changes in the resting membrane potential, without any effects on synaptic plasticity. Long-lasting aftereffects, on the other hand, seem to depend on synaptic modulation that is similar to long-term potentiation and long-term depression. Thus, aftereffects were associated with synaptic changes. Interestingly, aftereffects not only varied with different stimulation parameters such as current strength and total charge (stimulation strength (A)/electrode size (cm²) x total stimulation duration), but also with neurochemicals like dopamine, serotonin, and acetylcholine (Stagg & Nitsche, 2011). Serotonin was found to increase the magnitude and duration of aftereffects of facilitatory stimulation. Inhibitory tDCS was even turned into facilitatory by administering serotonergic medication (Nitsche et al., 2009). If these findings also apply to GVS, they are of great importance for its therapeutic use. Therapeutic effects could be enhanced by certain medications. For future studies, it would thus also be beneficial to assess patients' medication. Variations in medications could be responsible for differential effects of GVS. Since the administration of serotonergic medication is very common during the neurological rehabilitation process,

this could have led to variations in our study. However, further research is needed to confirm the effects of neurochemicals for GVS.

Despite the unexplained mechanisms of GVS-induced effects, the existence of such aforementioned aftereffects may have important implications for the use of GVS in the rehabilitation of neglect. So far, the placement of the electrodes for therapy was based on the effects observed during stimulation. Thus, neglect patients' counter-clockwise verticality deviations were ameliorated with a CL set-up (Saj et al., 2006). Due to our findings that verticality adjustments deviate towards the opposite, cathodal side for an extended period of time after stimulation (Study 2 & 3), it should be considered that both online and aftereffects could influence the therapeutic effect. While aftereffects of one session of GVS seem to be associated with the stimulation duration in a linear manner, it is not clear whether this is also true for repetitive GVS. In Study 3 we found that aftereffects on verticality perception exceeded the preceding stimulation duration: aftereffects up to at least 24 hours with a stimulation interval ranging from 3.3 to 4 hours. Two weeks after this assessment, at the FU1, the aftereffect had slightly decreased towards the baseline level again. Since this assessment was two weeks after the Post-test, it is not clear until when exactly the aftereffects in the subjective verticals persisted. Further studies are needed to investigate the exact time course of the aftereffects of repetitive GVS. Depending on the results, it might be useful to reconsider the placement of the electrodes to maximize the therapeutic effect.

Regarding aftereffects of GVS for spatial tasks, a recent study found that improvements of neglect symptoms lasted up to 4 weeks after CR-GVS. In Study 3, we also assessed aftereffects of GVS with spatial tasks, but found no differences in the improvements of both stimulation set-ups and the Sham group. One possible explanation for this might be a combination of subjects' head position and the type of task (discussed in greater detail in the following Chapter 3.2.2).

3.2.2 Differential effects depending on head position and spatial plane

In the two studies on GVS, stimulation had differential effects on the subjective verticals and a variety of spatial tasks. On the one hand, the subjective visual, haptic and postural vertical were influenced by GVS in healthy controls (Study 2) and right brain-damaged patients with neglect (Study 2 & 3). On the other hand, GVS did not influence various

spatial tasks (including reading, picture scanning, reading and drawing a clockface) more than standard therapy in neglect patients (Study 3).

One possible explanation for these discrepancies could be the combination of how GVS stimulated the vestibular system and the different planes the tasks were assessed in. As mentioned above, the subjects' head positioning determines which parts of the vestibular organs are stimulated during GVS. In both of our studies with GVS, subjects kept their head in an upright position. According to the vector model by Fitzpatrick and Day (2004) (see Chapter 1.2.3.2 for further details), GVS with the head upright mainly leads to a perception of head movement in the frontal plane (i.e. a head tilt) and a smaller movement in the horizontal plane (i.e. a turn of the head). Accordingly, the stimulation in our set-ups was predominantly taking place in the frontal plane. Consistent with that, we found GVS-induced changes in the visual, haptic and postural verticality adjustments. Spatial tasks which were administered in the horizontal plane were however not influenced since GVS only induced minor head movement perceptions in that plane. To conclude, the behavioral effects of GVS appear to be largely driven by the type of induced head movement. The spatial plane in which the induced head movements are most pronounced, seems to also be the plane in which the behavioral effects will be strongest.

Until now, variations in GVS-induced behavioral effects depending on the head position have only been investigated for subjects' posture and walking trajectories. When walking during GVS with the head pitched forward, subjects walked in a curved path towards the anode. With the head pitched backwards, their walking trajectories were curved towards the cathode. The extent of the deviation towards the side of the electrodes increased with a decrease of walking speed (Day & Fitzpatrick, 2005b). Furthermore, body movements to the left or right were stronger with the head upright than pitched forward due to the GVS-induced perception of head tilt. Such tilts cause body and/or leg movements to the sides to maintain the balance. Since with the head pitched forwards, subjects perceive head turns to the left or right, a balance response is not necessary (Fitzpatrick, Butler, & Day, 2006; St George & Fitzpatrick, 2011). Supporting these findings, GVS was reported to improve pusher behavior after a single session. During stimulation, patients held their head in an upright position and GVS hence induced head movement perceptions in the frontal plane. Since patients with pusher behavior seem to

have a deficit in the frontal plane (D. A. Perennou et al., 2008), GVS with the head upright might have been beneficial (Krewer et al., 2013).

Stronger movement perceptions in the horizontal plane are induced with GVS when the head is pitched forwards or backwards. The amount of the perceived movement depends on the extent of the head pitch. Accordingly, the influence of GVS on spatial tasks in the horizontal plane might be greater when subjects pitch their head forwards or backwards. Interestingly, all previous studies reporting improvements on spatial tasks in the horizontal plane administered the tasks on a table in front of the patients. To fulfill the tasks, patients must have looked down onto the paper, pitching their head forwards – at least slightly. GVS – which was applied simultaneously in all of these studies – might thus have induced a greater perception of head movement in the horizontal plane than with the head upright. Generally, greater improvements were found for a CR-GVS set-up (Rorsman et al., 1999; Utz, Keller, Kardinal, et al., 2011; Zubko et al., 2013). CR-GVS with the head slightly pitched forwards possibly induced head movement perceptions towards the cathode on the right, which in turn led to an actual head movement towards the left side. Both head and trunk movements (in the horizontal plane) towards the left are known to alleviate symptoms of neglect (Fujii, Fukatsu, Suzuki, & Yamadori, 1996; Schindler & Kerkhoff, 1997). The better left-sided performance in previous reports might thus have been mediated via head movements towards the left.

There are however also findings contradicting this line of reasoning. Utz, Keller, Kardinal, et al. (2011) also reported improvements on a line bisection task during CL-GVS. According to the aforementioned vector model, CL-GVS induces head movement perceptions towards the cathode on the left, but an actual head movement towards the anode on the right side. Based on this reasoning, CL-GVS would be expected to worsen and not improve left-sided performance.

Furthermore, one study demonstrated improvements in neglect patients' left arm position sense in the horizontal plane. Subjects' arm was passively moved with an arm position device and patients' were asked to indicate where their forefinger was positioned. While improvements were found up to 20 minutes post stimulation with CL-GVS, CR-GVS even worsened patients' arm position sense. Patients' head position during testing was not explicitly reported (Schmidt, Keller, et al., 2013). Since CL-GVS leads to bilateral brain activation (Dieterich et al., 2003; Fink et al., 2003), the authors suggested that such a

GVS-induced increase of overall activity of the brain might compensate for patients' large lesions and thus enhance improvements (Schmidt, Keller, et al., 2013).

Interestingly, a later study by the same group found that CR-GVS only worsened left arm position sense in right-handed healthy controls. Left-handed subjects were not affected by CR-GVS (Schmidt, Artinger, Stumpf, & Kerkhoff, 2013). In right-handed subjects CR-GVS leads to unilateral, right hemisphere activity (Fink et al., 2003). Thus, it appears that activating the right hemisphere worsens left arm position sense. It is not entirely clear though why this is the case. Due to the lack of studies on GVS in left-handed subjects, it can only be hypothesized that CR-GVS would lead to bilateral activity. Such bilateral activation pattern in left-handers was previously reported using caloric irrigation (Dieterich et al., 2003). Hence, bilateral activation would only lead to an overall increase in activation, but not to a change of the interplay between the two hemispheres. This would explain, why left-handers are not affected by CR-GVS. However, further neuroimaging studies are needed to investigate GVS-induced brain activity in left-handed subjects.

If the therapeutic effects of GVS are directly related to the spatial plane in which GVS induces head movement perceptions, the transfer of improvements from one spatial plane to another is an important issue. Until now, there are no studies investigating such a transfer after the application of GVS. Our findings from Study 3 do not indicate a transfer from improvements on the subjective visual and haptic vertical to spatial tasks of the NET. To our knowledge, there is only one study investigating such a transfer so far. Funk et al. (2013) led patients perform a feedback-based, computerized training of visual line orientation over 4 weeks. The training consisted of tasks in the frontal plane. They authors did not only find improvements in trained orientation tests, but also a transfer to untrained spatial tasks that partly were administered in the horizontal plane. These tasks were related to orientation perception, such as horizontal writing, analog clock reading, and visuo-constructive capacities. Improvements were still stable at a 2-month follow-up. No improvements were found for visual tasks unrelated to orientation discrimination.

3.2.3 Stimulation and plasticity in the lesioned brain

Due to the lack of studies, it is unknown whether GVS actually has the same physiological effects and activates the same brain areas (see Chapter 1.2.3.3 for further details) in the damaged brain compared to the healthy brain. It is however assumed that the same areas – if they are spared by the lesion – are also activated in brain-damaged patients. Supporting this, similar activations to those known from healthy controls were found during a visuospatial exploration task in recovered, right brain-damaged patients (Pizzamiglio et al., 1998).

A couple of studies have investigated the effects of tDCS in the damaged brain. A computer-based model revealed elevated current density maxima in three different stroke models. The location of the current density maxima was also altered, and located directly along the stroke border or more inferior along the cortical surface. Moreover the cerebral spinal fluid in the infarction region led to a different conduction of the currents (Wagner et al., 2007). This indicates that stimulation in brain damaged patients might have different effects than in healthy controls. That these effects could still be promising was demonstrated by a study on rats. Anodal tDCS led to improved motor function and a reduced white matter axon deterioration. Despite a lacking influence on the size of the actual infarct areas, these findings indicate a possible neuroprotective effect of brain stimulation (Kim et al., 2010). It has to be considered though that tDCS is applied directly over the cortex and could thus lead to differential effects compared to GVS that is applied in the periphery.

Regarding plasticity after structural and functional brain damage, research from various fields has reported different mechanisms of plasticity: the redistribution of damaged cortical representations to neighbouring or remote areas, the sprouting of new, and the regeneration of old afferents (for reviews see Duffau, 2006; Kaas & Florence, 1997; Stein & Hoffman, 2003). Recently, functional connectivity was shown to only recover with intact, but not disrupted, anatomical connections (He et al., 2007). Similarly, neglect patients' brain activity patterns were found to partly restore and rebalance. These changes were correlated with the recovery of attentional deficits (Corbetta et al., 2005).

3.3 Conclusions

This thesis demonstrates that neglect is a complex, multi-faceted disorder. The nature of its deficits includes spatial, verticality, and temporal deficits. Within the framework of this work, spatial and temporal processing were shown to be related. This association and the variety of deficits might be a result of the fact that the brain areas affected in neglect serve various, multimodal functions.

Regarding the treatment of neglect-related deficits, GVS appears to be a promising candidate since it activates vestibular cortical areas which are known to be involved in both spatial and verticality processing. As part of this thesis, two projects demonstrated that GVS is indeed affecting verticality perception both during and after its application. However, GVS only exerted a minor influence on spatial perception – at least when combined with standard therapy.

Taken together, these two findings imply that the vestibular processing areas share a greater overlap with the cortical areas for verticality perception than with the spatial processing areas. However this is not to say that GVS may not have therapeutic value for the treatment of spatial deficits. In particular it should be noted that there is a possibility that certain conditions (e.g. head position) might produce better alignment of the pathways activated by a given task and the pathways stimulated by GVS, and so enhance the effectiveness of GVS.

3.4 Future directions

The primary motivation for this work was the idea that understanding neglect may lead to the development of treatments which mitigate the effect of neglect on rehabilitation. While this work has provided new scientific insight and brought us a step closer to this goal, there are still many outstanding issues which are not yet understood. Here we discuss a few particularly relevant avenues for future research.

Our findings that GVS has different effects on different types of tasks emphasizes the importance of further investigations on the underlying mechanisms of GVS. It is therefore necessary to clarify how the effects of GVS, the induced head movement perception, and the spatial plane a given task is assessed in are related. If these aspects are closely associated then GVS could potentially have a greater therapeutic effect on spatial

deficits than has previously been shown. Additionally it would be interesting to explore a potential effect of GVS on temporal perception and deficits.

Another important question concerns the brain activity that is induced by GVS in brain-damaged patients. Neuroimaging studies would be extremely helpful not only in extending the scientific knowledge about electrical stimulation, but would also have direct implications for the therapeutic use of GVS.

Regarding the therapeutic application of GVS in neglect, the answer to the following questions is crucial: a) what is the exact time course of GVS aftereffects, b) how are the current intensity relate to the effect magnitude, and c) the frequency of stimulation related to the effect magnitude. One promising possibility could be the use of GVS at an early stage of the rehabilitation process, when patients are still too impaired to benefit from other treatments that require general alertness and attentional resources.

Since GVS seems to have the potency to induce lasting changes in behavior, further research would be highly relevant for the field of neuroscience and neurorehabilitation.

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Appendix

Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation „Processing of time and space in visuo-spatial neglect and the influence of galvanic vestibular stimulation“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “Processing of time and space in visuo-spatial neglect and the influence of galvanic vestibular stimulation” is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 02.05.2014

Katharina Volkening

Contributions

Study 1 (submitted)

K. Volkening, V. Flanagan, I. Keller (submitted).

Time estimation and bisection of multi-second intervals in right brain-damaged patients. IK conceived of the study, conducted the stimulus material and lesion maps, contributed to the interpretation of the results and revised the manuscript. KV helped with the design of the study, recruited the participants, collected the data, performed analyses and interpretation of data and wrote the manuscript. VF helped with additional statistical analysis (Regression line slopes) contributed to the interpretation of the results and revised the manuscript.

Study 2 (submitted)

K. Volkening, J. Bergmann, I. Keller, F. Müller, K. Jahn (submitted).

Verticality perception during and after galvanic vestibular stimulation.

KV and JB (joint first authors) designed the study, recruited the participants, collected the data, performed analyses and interpretation of data and wrote the manuscript. IK, FM, JK contributed to the interpretation of the results and revised the manuscript.

Study 3

K. Volkening, G. Kerkhoff, I. Keller

GK: conceived of the study and revised the manuscript. IK conceived of the study, collected data (at Post, FU1 & FU2), contributed to the interpretation of the results and revised the manuscript. KV designed and coordinated the study, recruited the participants, performed the therapy, collected data (at baseline), performed analyses and interpretation of data and wrote the manuscript.

I hereby confirm the above mentioned contributions to the dissertation "Processing of time and space in visuo-spatial neglect and the influence of galvanic vestibular stimulation".

Bad Aibling, 21.02.2014

Prof. Ingo Keller

Bad Aibling, 21.02.2014

M.Sc. Jeannine Bergmann
(Joint first author Study 2)

